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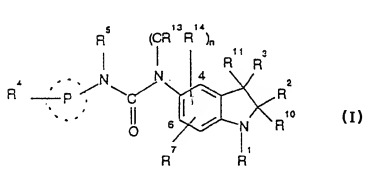
(54) Title: CONDENSED INDOLE DERIVATIVES AS $5HT_{2C}$ AND $5HT_{2B}$ ANTAGONISTS



(I)

(57) Abstract

Compounds of formula (I) or a salt thereof wherein: P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur; R^1 is hydrogen or C_{1-6} alkyl; R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain; R^4 is hydrogen, C_{1-6} alkyl, halogen, NR^8R^9 or OR^{12}, where R^8, R^9 and R^{12} are independently hydrogen or C_{1-6} alkyl; R^5 is hydrogen or C_{1-6} alkyl; R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl; n is 2 or 3; and the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl, are $5HT_{2C}/5HT_{2B}$ receptor antagonists and are of potential use in the treatment of CNS disorders such as anxiety.

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Condensed indole derivatives as $5HT_{2D}$ and $5HT_{2B}$ antagonists

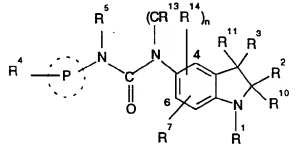
This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

P. Fludzinski et. al., J. Med. Chem. 1986 29 2415-2418 describes N-(1,2-dimethyl-3-ethyl-1H-indol-5-yl)-N'- (3-trifluoromethylphenyl)urea which shows selectivity for the rat stomach fundus serotonin receptor.

WO 92/05170 describes certain urea derivatives which are described as possessing $5HT_{1C}$ receptor antagonist activity. The $5HT_{1C}$ receptor has recently been reclassified as the $5HT_{2C}$ receptor [P. Hartig et al., Trends in Pharmacological Sciences (TIPS) 1993].

A structurally distinct class of compounds has now been discovered, which compounds have been found to have $5HT_{2C}$ receptor antagonist activity. Certain compounds of the invention also show $5HT_{2B}$ receptor antagonist activity, the $5HT_{2B}$ receptor being previously known as the fundus receptor [P.Hartig et al., Trends in Pharmacological Sciences (TIPS) 1993]. $5HT_{2C}$ /$5HT_{2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or a salt thereof:



(I)

wherein:

P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain;

R^4 is hydrogen, C_{1-6} alkyl, halogen, NR^8R^9 or OR^{12}, where R^8, R^9 and R^{12} are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl; and

n is 2 or 3; and

the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl.

C_{1-6} alkyl moieties can be straight chain or branched and are preferably C_{1-3} alkyl, such as methyl, ethyl, n- and iso- propyl.

Suitable R^4 and R^7 halogens include chloro and bromo.

Suitably R^1 is hydrogen or C_{1-6} alkyl such as methyl, ethyl or propyl. Preferably R^1 is methyl or ethyl.

Suitably R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain. Preferably R^2 is hydrogen or methyl. Preferably R^3 is hydrogen.

In an indoline structure, R^{10} and R^{11} are preferably hydrogen. Most preferably R^{10} and R^{11} form a bond so as to give an indole structure.

Suitably R^4 is hydrogen, C_{1-6} alkyl, halogen, NR^8R^9 or OR^{12}, where R^8, R^9 and R^{12} are independently hydrogen or C_{1-6} alkyl. Preferably R^4 is hydrogen or methyl.

Suitably R^5 is hydrogen or C_{1-6} alkyl. Preferably R^5 is hydrogen.

Suitably R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl. The group R^7 can be attached to any vacant position in the phenyl part of the indole or indoline rings, that is to say, the 4-, 6- or 7-positions of the indole or indoline rings. Preferably R^7 is hydrogen.

Suitably P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur. Suitable moieties when the ring P is a 5-membered aromatic heterocyclic ring include, for example, isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. Suitable moieties when the ring P is a 6-membered aromatic heterocyclic ring include, for example, pyridyl, pyrimidyl or pyrazinyl. When P is a quinoline or isoquinoline residue, the urea moiety can be attached at any position of the ring, preferably to the 4-position.

Preferably P is a 4-quinoline or 3-pyridyl group.

The urea moiety can be attached to a carbon or any available nitrogen atom of the ring P, preferably it is attached to a carbon atom.

Suitably the group $-(CR^{13}R^{14})_n-$ forms an ethylene or propylene group each of which can be substituted by C_{1-6}alkyl. The group $-(CR^{13}R^{14})_n-$ can be attached to the 4- or 6-position of the indole or indoline ring, preferably it is attached to the

6-position. Preferably the group -$(CR^{13}R^{14})_n$- is ethylene.

Particularly preferred compounds of formula (I) include:

5-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6-Methyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
5,7-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6-Methyl-3-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
6-Methyl-3-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
5-Methyl-1-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-Methyl-1-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-Methyl-1-(3-pyridylcarbamoyl)-2,3,6,7-tetrahydropyrrolo[2,3-f]indole
5-Ethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-n-Propyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5,6-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6,7-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
1-Methyl-N-(3-pyridyl)-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline-5-carboxamide
3-Methyl-N-(3-pyridyl)-6,7,8,9-tetrahydro-3H-pyrrolo[3,2-f]quinoline-6-carboxamide
6-Methyl-3-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole,
6-Methyl-3-(5-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole,
6-Methyl-3-(3-quinolinylcarbamoyl)-2,3-dihydropyrrolo [3,2-e]indole,
5-Methyl-1-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole,
6,8-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole,
6-Methyl-3-(3-pyridylcarbamoyl)-2,3,7,8-tetrahydropyrrolo[3,2-e]-indole,
5-Methyl-1-(2-pyrazinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[3,2-e]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(5-quinolylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isoxazolylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
N-(5-Isoquinolyl)-5-methyl-2,3-dihydropyrrolo[2,3-f] indole-1-carboxamide,
N-(6-Quinolyl)-5-methyl-2,3-dihydro-pyrrolo [2,3-f]indole-1-carboxamide;
or pharmaceutically acceptable salts thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

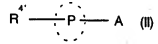
Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

When R^1 (in an indole) and/or R^5 are hydrogen or when R^4 is hydroxy or NR^8R^9 and at least one of R^8 and R^9 are hydrogen the compounds of formula (I) may exist tautomerically in more than one form. The invention extends to these and any other tautomeric forms and mixtures thereof.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

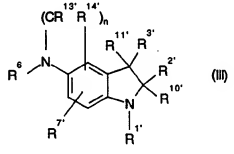
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

(a) the coupling of a compound of formula (II);



(II)

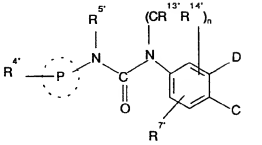
with a compound of formula (III);



(III)

wherein A and R^6 contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is R^5 as defined in formula (I) or a group convertible thereto, n is as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ are R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4 and R^7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5, and R^7 respectively to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt thereof;

or (b) cyclising a compound of formula (IV):



(IV)

wherein $R^{4'}$, $R^{5'}$, $R^{7'}$, $R^{13'}$, and $R^{14'}$ are as defined in formulae (II) and (III), n is as defined in formula (I), and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$ and $R^{11'}$ as defined in formula (III), and thereafter optionally and as necessary in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt.

Suitable examples of groups A and R^6 include:

(i) A is -N=C=O and R^6 is -H,

(ii) A is $-NR^{5'}COL$ and R^6 is -H,

(iii) A is $-NHR^{5'}$ and R^6 is COL, or

(iv) A is halogen and R^6 is $-CONHR^{5'}$,

wherein $R^{5'}$ is as defined above and L is a leaving group. Examples of suitable leaving groups L include imidazole, halogen such as chloro or bromo or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and R^6 is H the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is $-NR^{5'}COL$ and R^6 is H or when A is $-NHR^{5'}$ and R^6 is COL, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and R^6 is $CONHR^{5'}$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

The cyclisation of the compound of formula (IV) to prepare indoles (R^{10} and R^{11} are a bond) may be effected using standard methodology such as described in

Comprehensive Heterocyclic Chemistry 1984 **4**, 313 **et. seq.** or J. Het. Chem. 1988 **25** p.1 **et seq**.

Examples of the more important routes include the Leimgruber synthesis, the Fischer synthesis, the Japp-Klingemann variation, the Madelung synthesis and the Nordlander synthesis.

Examples of the groups C and D in the preparation of indoles include:

(v) C is NO_2 and D is $CH{=}CH\text{-}NZ_2$ where each Z is independently C_{1-6} alkyl or together represent C_{2-7} alkylene;

(vi) C is $NR^{1'}\text{-}N{=}C(R^{2'})\text{-}CH_2R^{3'}$ and D is H;

(vii) C is $NH\text{-}N{=}C(CO_2X)\text{-}CH_2R^{3'}$ and D is H where X is C_{1-6} alkyl;

(viii) C is $NR^{1'}COR^{2'}$ and D is $CH_2R^{3'}$.

(ix) C is $NHCH_2CR^{3'}(OR)_2$ and D is H where R is a C_{1-6}alkyl group.

Indolines may also be prepared by reduction, e.g. with $NaCNBH_3$, of indoles produced by variants (vi) to (ix) above.

In reaction variant (v) (Leimgruber synthesis) the compound of formula (IV) is prepared from the 2-methylnitrophenyl urea by treatment with a dialkylacetal of the dialkylformamide $OHCNZ_2$ with heating and the product of formula (IV) cyclised by hydrogenation over a suitable catalyst such as palladium and charcoal optionally under pressure to yield the compound of formula (I) where $R^1{=}R^2{=}R^3{=}H$.

In reaction variant (vi) (Fischer synthesis) the compound of formula (IV) is prepared from the hydrazinophenyl urea by dehydration, preferably by heating, with the appropriate ketone $R^{2'}COCH_2R^{3'}$ and the product of formula (IV) cyclised by heating with an acid catalyst such as hydrochloric or sulphuric acid.

In reaction variant (vii) (Japp-Klingemann synthesis) the compound of formula (IV) is prepared from the aminophenyl urea by diazotisation followed by treatment for example with $CH_3COCH(CO_2X)\text{-}CH_2R^{3'}$ where X is C_{1-6} alkyl under basic conditions in aqueous alcohol as solvent.

The product of formula (IV) may then be cyclised as in the Fischer synthesis above.

In reaction variant (viii) (Madelung synthesis) the compound of formula (IV) is cyclised with base in an inert solvent optionally with heating.

In reaction variant (ix) (Nordlander synthesis), the compound of formula (IV) is cyclised by heating in a mixture of trifluoroacetic anhydride/acid.

It will be appreciated that when D is hydrogen, either or both indole isomers may be formed during the cyclisation process.

Suitable examples of groups $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{7'}$ which are convertible to R^2, R^3, R^4, and R^7 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When R^4 is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyl which is removed by hydrogenation.

Suitable examples of a group $R^{1'}$ which is convertible to R^1, include typical N-protecting groups such as alkoxycarbonyl, in particular t-butyloxycarbonyi, acetyl, trifluoroacetyl, benzyl and **para**-methoxybenzyl which are converted to R^1 hydrogen using conventional conditions.

Suitable examples of a group $R^{5'}$ which is convertible to R^5 include alkoxycarbonyl and benzyl or **para**-methoxybenzyl which are converted to R^5 is hydrogen using conventional conditions.

Interconversions of R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7 are carried out by conventional procedures.

For example, in the case wherein R^1, R^2 and R^3 are C_{1-6} alkyl and R^5 is hydrogen it is possible to introduce a C_{1-6} alkyl group at the R^5 position by conventional alkylation using 1 molar equivalent of a C_{1-6} alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. R^1 C_{1-6} alkyl groups may also be introduced by conventional alkylation, for example using a C_{1-6} alkyl halide and base such as sodium hydride, or by reduction of C_{1-6} acyl.

R^4 halo and R^7 halo may be introduced by selective halogenation of the ring P or indole/indoline ring respectively using conventional conditions.

It should be appreciated that it may be necessary to protect any R^1 to R^{12} hydrogen variables which are not required to be interconverted.

Protection, especially of a $R^{1'}$ hydrogen, may also be necessary during coupling reaction (a) and ring-forming reaction (b) above.

Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

It is preferable, however, to introduce and interconvert the groups R^1 to R^{12} before coupling compounds of formulae (II) and (III) together, or cyclising the compound of formula (IV).

Compounds of formula (I) which are substituted indoles, and their appropriate derivatives, can be converted to the corresponding indolines, and vice versa, by

conventional methods, e.g. reduction with $NaCNBH_3$ in acetic acid and oxidation using MnO_2 in an inert solvent.

Compounds of formula (II) in which A is $NHR^{5'}$ are known compounds or can be prepared analogously to known compounds, see, for example, WO 92/05170.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

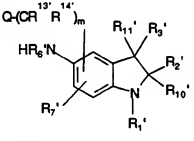
ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov et al, Helv. Chim. Acta 1987 70 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $-NR^{5'}COL$ may be prepared by reacting a compound of formula (II) in which A is $-NHR^{5'}$ with phosgene or a phosgene equivalent, in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as triethylamine.

Compounds of formula (III) may be prepared:

(a) by cyclisation of compounds of formula (V), followed by reduction to the amine if necessary

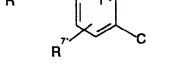


(V)

wherein Q is $CR^{13}R^{14}L$, $CR^{13}O$ or CO_2R where L is a leaving group and R^{13} and R^{14} are as defined in formula (I), m is 1 or 2, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{7'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$ and $R^{14'}$ are as defined in formula (III) above, $R^{6'}$ is a group R^6 as defined in formula (III) and R is an aryl or

C_{1-6}alkyl group,

or (b) cyclisation of compounds of formula (VI)



(VI)

wherein , $R^{6'}$, $R^{7'}$, $R^{13'}$, $R^{14'}$ and n are as defined in formula (V) and C and D are as defined in formula (IV) above.

The cyclisation of a compound of formula (V) may be suitably carried out in an inert solvent at ambient or elevated temperatures, optionally in the presence of a base. Reduction may be carried out using conventional reduction techniques. The cyclisation of a compound of formula (VI) may be suitably carried out using the procedures outlined for the cyclisation of a compound of formula (IV), above.

Compounds of formula (II) in which A is halogen and $R^{4'}$ is hydrogen are commercially available.

Novel intermediates of formulae (III) and (IV) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2C}$ receptor antagonist activity, and certain compounds show $5HT_{2B}$ antagonist activity. Compounds of formula (I) are therefore believed to be of potential use in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders,

injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The following Descriptions illustrate the preparation of intermediates to compounds of the present invention.

Description 1

1-Acetyl-5-aminoindoline (D1)

1-Acetyl-5-nitroindoline (12.77g, 62 mmol), cyclohexene (62 ml, 610 mmol), and 5% palladium on charcoal (2.34g) were stirred at reflux under nitrogen for 18h. A further portion of catalyst (0.5g) was then added, and reflux was continued for a further 3h. The mixture was cooled, filtered through Kieselguhr, and evaporated to give the title compound (9.33g, 85%) as an orange-yellow solid.

NMR (D_6-DMSO) δ: 2.05 (3H, s), 3.0 (2H, t, J 8), 3.97 (2H, t, J 8), 4.97 (2H, bs), 6.33 (1H, dd, J 7,1), 6.46 (1H, d, J 1), 7.72 (1H, d, J 7).

Description 2

N-(1-Acetyl-5-indolinyl)-2,2-diethoxyethylamine (D2)

1-Acetyl-5-aminoindoline (D1) (9.33g, 53 mmol), bromoacetaldehyde diethyl acetal (6.0 ml, 40 mmol) and sodium hydrogen carbonate (4.58g, 54 mmol) was stirred at reflux under nitrogen for 64h. Further acetal (2.0 ml, 13 mmol) was then added, and reflux was continued for a further 24h. The mixture was cooled, filtered, and evaporated to near-dryness. Chromatography on silica gel using ethyl acetate/petroleum ether (b.p. 60-80°C) (50-100% ethyl acetate) gave the title compound (6.59g) as a yellow-brown solid, in addition to recovered starting amine (3.09g). The yield of product was 63%, based on consumed starting material.

NMR ($CDCl_3$) δ: 1.25 (6H, t, J 7), 2.2 (3H, s), 3.13 (2H, t, J 8), 3.22 (2H, d, J 5), 3.5-3.65 (2H, m), 3.65-3.8 (2H, m), 4.01 (2H, t, J 8), 4.68 (1H, t, J 5), 6.5 (2H, m), 8.03 (1H, d, J 7).

Alternative Procedure

1-Acetyl-5-aminoindoline (D1) was reductively alkylated with glyoxal monomethyl acetal in ethanol at 45°C using 10% palladium on charcoal and hydrogen at 50 p.s.i. Removal of the catalyst by filtration followed by evaporation of the solvent afforded the corresponding dimethyl acetal which was used directly in Description 3 instead of the diethyl acetal.

Description 3

1-Acetyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D3)

N-(1-Acetyl-5-indolinyl)-2,2-diethoxyethylamine (D2) (6.51g, 22 mmol) was added to an ice-cold, stirred mixture of trifluoroacetic acid (25 ml) and trifluoroacetic anhydride (25 ml). The mixture was stirred at 0°C under nitrogen for 0.5h, after which time further trifluoroacetic acid (40 ml) was added. The mixture was then heated at reflux for 64h, cooled, and evaporated to dryness. Chromatography on silica gel using ethyl acetate/chloroform (0-60% ethyl acetate) then gave the title compound (6.28, 89%) as a light cream solid which darkened slightly on standing.

NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.37 (2H, t, J 8), 4.17 (2H, t, J 7), 6.76 (1H, d, J 3), 7.45 (1H, m), 8.27 (1H, s), 8.44 (1H, s).

Description 4

1-Acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4)

1-Acetyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D3) (2.80g, 9.4 mmol) was suspended with stirring in methanol (100 ml), and anhydrous potassium carbonate (1.96g, 14.2 mmol) was added. The mixture was stirred for 0.5h, evaporated to near-dryness, and partitioned between ethyl acetate and water. After separation, the aqueous portion was extracted with 5% methanol/chloroform, and the combined organics were dried (Na_2SO_4), filtered and evaporated, giving the title compound (1.53g, 80%) as a cream solid.

NMR (D_6-DMSO) δ: 2.15 (3H, s), 3.18 (2H, t, J 8), 4.08 (2H, t, J 8), 6.33 (1H, bs), 7.2 (2H, m), 8.22 (1H, s), 10.9 (1H, bs).

Description 5

1-Acetyl-5-methyl-2,3-dihydropyrrolo[2,3-f]indole (D5)

Sodium hydride (80%, 0.25g, 8.3 mmol) was stirred under nitrogen in dry N,N-dimethylformamide (DMF) (5 ml), as 1-acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4) (1.52g, 7.6 mmol) was added in DMF (20 ml), with effervescence. The mixture was stirred for 0.5h, and iodomethane (0.52 ml, 8.3 mmol) was then added in DMF (5 ml). After stirring for a further 1h, excess sodium hydride was quenched by addition of water (1 ml), and the mixture was partitioned between ethyl acetate and water, and separated. The organic portion was washed with water and brine, dried (Na_2SO_4) and evaporated. Chromatography on silica gel using ethyl acetate/chloroform (0-50% ethyl acetate) then gave the title compound (0.80g, 49%) as a pale yellow solid.

NMR ($CDCl_3$) ca.5:1 mixture of rotamers δ:
2.26 (major, 3H, s), 2.51 (minor, 3H, s), 3.16 (minor, 2H, t, J 8), 3.3 (major, 2H, t, J 8), 3.74 (major, 3H, s), 3.77 (minor, 3H, s), 4.1 (major, 2H, t, J 8), 4.19 (minor, 2H, t, J 8), 6.44 (both, 1H, d, J 2), 6.98 (major, 1H, d, J 2), 7.0 (minor, m), 7.09 (major, 1H, s), 7.18 (minor, 1H, s), 7.31 (minor, 1H, s), 8.48 (major, 1H, s).

Description 6

5-Methyl-2,3-dihydropyrrolo[2,3-f]indole (D6)

1-Acetyl-5-methyl-2,3-dihydropyrrolo[2,3-f]indole (D5) (0.70g, 3.3 mmol) was stirred at reflux under nitrogen in 10% sodium hydroxide solution (50 ml) for 4h. The mixture was cooled, diluted with water (200 ml), and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give the title compound (0.58g) as a light brown gum, still containing ca. 20% of the starting amide (NMR). This material was used in the next step without purification.

NMR ($CDCl_3$) δ: 3.12 (2H, t, J 9), 3.33 (1H, bs), 3.56 (2H, t, J 9), 3.7 (3H, s), 6.27 (1H, d, J 3), 6.85 (1H, s), 6.9 (1H, d, J 3), 7.08 (1H, s).

Description 7

(1-Methyl-5-nitro-4-indolyl)acetonitrile (D7)

1-Methyl-5-nitroindole (0.77g, 4.4 mmol) and (4-chlorophenoxy)acetonitrile (0.88g, 5.2 mmol) were stirred in dry DMF (10 ml) at 0°C, and potassium t-butoxide (1.47g, 13.1 mmol) was added in dry DMF (10 ml). The mixture was stirred at 0°C for 15 min, poured into 1M hydrochloric acid (200 ml), and stirred until the precipitate coagulated. The solid was then filtered off and dried. Chromatography on silica gel using chloroform then gave the title compound (0.48g, 51%) as a yellow solid.

NMR ($CDCl_3$) δ: 3.9 (3H, s), 4.37 (2H, s), 6.78 (1H, d, J 3), 7.31 (1H, d, J 3), 7.38 (1H, d, J 8), 8.12 (1H, d, J 8).

Description 8

2-(1-Methyl-5-nitro-4-indolyl)ethanol

(1-Methyl-5-nitro-4-indolyl)acetonitrile (D7) (3.36g, 15.6 mmol) was stirred in dry tetrahydrofuran (THF) (100 ml) under nitrogen, as diisobutylaluminium hydride (1.5M in toluene, 21 ml, 31.5 mmol) was added. The mixture was stirred for 6h, and methanol (25

ml) was added. After a further 5 min, it was diluted with water (500 ml), acidified with 5M hydrochloric acid, and extracted with chloroform. The extract was dried (Na_2SO_4), evaporated to a blackish gum, and suspended in ethanol (100 ml). Sodium borohydride (0.88g, 23.1 mmol) was added, and the mixture was stirred for 0.5h, when a second similar portion of sodium borohydride was added. After a further 0.5h, the mixture was diluted with water (500 ml), acidified with 5M hydrochloric acid, and extracted with chloroform. The extract was washed with brine, dried (Na_2SO_4) and evaporated to a brown gum. Chromatography on silica gel using ethyl acetate/petroleum ether (b.p. 60-80°C) (20-60% ethyl acetate) gave the title compound (0.50g, 15%) as a brown oil.

NMR ($CDCl_3$) δ: 3.47 (2H, t, J 7), 3.78 (3H, s), 4.02 (2H, t, J 7), 6.73 (1H, d, J 3), 7.2 (2H, m), 7.89 (1H, d, J 8).

Description 9

2-(1-Methyl-5-nitro-4-indolyl)ethyl methanesulphonate (D9)

2-(1-Methyl-5-nitro-4-indolyl)ethanol (D8) (0.50g, 2.3 mmol) and triethylamine (0.38 ml, 2.7 mmol) were stirred in dichloromethane (10 ml), and methanesulphonyl chloride (0.21 ml, 2.7 mmol) was added. The mixture was stirred for 10 min, when water (10 ml) was added, and then stirred vigorously for a further 10 min. After acidification with 5M hydrochloric acid, the layers were separated, and the organic portion was dried (Na_2SO_4) and evaporated to give a dark oil. Chromatography on silica gel using chloroform followed by dichloromethane gave the title compound (0.54g, 79%) as an orange solid.

NMR ($CDCl_3$) δ: 2.44 (3H, s), 3.68 (2H, t, J 7), 3.85 (3H, s), 4.63 (2H, t, J 7), 6.81 (1H, d, J 3), 7.25 (1H, d, J 3), 7.3 (1H, d, J 8), 8.0 (1H, d, J 8).

Description 10

6-Methyl-2,3-dihydropyrrolo[3,2-e]indole (D10)

2-(1-Methyl-5-nitro-4-indolyl)ethyl methanesulphonate (D9) (0.38g, 1.3 mmol) was hydrogenated over 5% palladium on charcoal (0.23g) in dry DMF (20 ml) at 80 p.s.i. H_2 for 2h, diluted with ethanol (80 ml), filtered through Kieselguhr, and evaporated to a brown gum. The title compound can be purified by preparation of the HCl salt to give 6-Methyl-2,3-dihydropyrrolo[3,2-e]indolehydrochloride.

Description 11

N-(1-Acetyl-5-indolinyl)-2-chloroallylamine (D11)

1-Acetyl-5-aminoindoline (D1) (4.36g, 24.8 mmol), anhydrous potassium carbonate (5.1g, 37 mmol) and 2,3-dichloro-1-propene (4.5 ml, 48.9 mmol) were stirred in dry DMF (50 ml) at 70°C for 16 h. The mixture was then diluted with water (500 ml), and stirred for 10 min. Filtration and air drying then gave the title compound (5.71g, 92%) as a dark olive solid.

NMR ($CDCl_3$) δ 2.19 (3H, s), 3.13 (2H, t, J 8), 3.9-4.2 (5H, m), 5.32 (1H, m), 5.41 (1H, m), 6.4-6.6 (2H, m), 8.05 (1H, d, J 9)

Description 12

N-(1-Acetyl-5-indolinyl)-2-chloro-N-trifluoroacetylallylamine (D12)

N-(1-Acetyl-5-indolinyl)-2-chloroallylamine (D11) (5.71g, 24.8 mmol) and triethylamine (3.8 ml, 27.3 mmol) were stirred in chloroform (100 ml), and trifluoroacetic anhydride (3.8 ml, 27.3 mmol) was added dropwise over 1 min. The mixture was stirred for 1 h, when water (100 ml) was added. This mixture was stirred vigorously for 20 min, acidified with 5 M hydrochloric acid, and separated. The organic portion was dried (Na_2SO_4) and evaporated to give the title compound as a dark oil (7.49 g, 95%), which solidified on standing.

NMR ($CDCl_3$) δ : 2.25 (3H, s), 3.24 (2H, t, J 8), 4.16 (2H, t, J 8), 4.52 (2H, s), 5.23 (1H, s), 5.36 (1H, s), 7.1 (2H, m), 8.23 (1H, d, J 8)

Description 13

1 Acetyl-7-methyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D13)

N-(1-Acetyl-5-indolinyl)-2-chloro-N-trifluoroacetylallylamine (D12) (7.63 g, 22 mmol) was stirred in polyphosphoric acid (38 g) at 140° C for 1.5h. The mixture was cooled, dispersed in water (200 ml) and extracted with ethyl acetate. The extract was filtered through Kieselguhr, dried (Na_2SO_4) and evaporated to give a dark gum (ca. 3g). Chromatography on silica gel, eluting with 0-20% ethyl acetate in chloroform gave the title compound (0.49g, 7%) as a light yellow solid.

NMR ($CDCl_3$) δ : 2.28 (3H, s), 2.33 (3H, s), 3.36 (2H, t, J 8), 4.18 (2H, t, J 8), 7.19 (1H, s), 8.24 (1H, s), 8.36 (1H, s).

Description 14

1-Acetyl-7-methyl-2,3-dihydropyrrolo[2,3-f]indole (D14)

This was prepared from 1-acetyl-7-methyl-5-trifluoroacetyl-2,3-dihydropyrrolo[2,3-f]indole (D13) (0.49g, 1.58 mmol) following the procedure of Description 4, but working up by dilution with water. The title compound (0.31g, 91%) was then isolated by filtration and drying, as a yellow solid.

NMR (D_6-DMSO) δ : 2.15 (3H, s), 2.18 (3H, s), 3.17 (2H, t, J 8), 4.09 (2H, t, J 8), 7.00 (1H, s), 7.14 (1H, s), 8.16 (1H, s), 10.55 (1H, b s)

Description 15

1-Acetyl-5,7-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D15)

This was prepared from 1-acetyl-7-methyl-2,3-dihydropyrrolo[2,3-f]indole (D14) (0.31g, 1.46 mmol) following the procedure of Description 5, but working up by dilution with water. The title compound (0.26g, 79%) was then isolated by filtration and drying, as an orange-yellow solid.

NMR ($CDCl_3$) ca 5:1 mixture of rotamers, δ :
2.27 & 2.30 (major, 3H, s + both, 3H, s), 2.53 (minor, 3H, s), 3.15 (minor, 2H, t, J 8), 3.30 (major, 2H, t, J 8), 3.68 (major, 3H, s), 3.70 (minor, 3H, s), 4.10 (major, 2H, t, J 8), 4.20 (minor, 2H, t, J 8), 6.76 (major, 1H, s), 6.80 (minor, 1H, s), 7.05 (major, 1H, s), 7.13 (minor, 1H, s), 7.19 (minor, 1H, s), 8.42 (major, 1H, s).

Description 16

5,7-Dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D16)

This was prepared from 1-acetyl-5,7-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D15) (0.44g, 1.93 mmol) following the procedure of Description 6, using 5:1 10% sodium hydroxide solution/ethanol as solvent. NMR after 7h reaction time showed ca. 60% reaction, but this material (0.30g) was used in the next step without separation of the starting material.

Description 17

1-Acetyl-5-ethyl-2,3-dihydropyrrolo[2,3-f]indole (D17)

The title compound was prepared from 1-acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4), sodium hydride and ethyl iodide in 90% yield using a procedure similar to that for D5.

NMR ($CDCl_3$) (mixture of rotamers) δ major signals:
1.44 (3H, t, J 8), 2.23 (3H, s), 3.29 (2H, t, J 10), 4.0-4.25 (4H, m), 6.43 (1H, d, J 3), 7.03 (1H, d, J 3), 7.10 (1H, s), 8.48 (1H, s)

Description 18

5-Ethyl-2,3-dihydropyrrolo[2,3-f]indole (D18)

The title compound was prepared from 1-acetyl-5-ethyl-2,3-dihydropyrrolo[2,3-f]indole (D17) in 100% yield using a procedure similar to that for D6.

NMR ($CDCl_3$) δ: 1.41 (3H, t, J 8), 3.12 (2H, t, J 10), 3.58 (2H, t, J 10), 4.08 (2H, q, J 8), 6.26 (1H, d, J 3), 6.84 (1H, s), 6.97 (1H, d, J 3), 7.12 (1H, s)

Description 19

1-Acetyl-5-n-propyl-2,3-dihydropyrrolo[2,3-f]indole (D19)

Prepared as in Description 5 using sodium hydride (80%, 0.08g, 2.8 mmol), 1-acetyl-2,3-dihydropyrrolo[2,3-f]indole (D4) (0.4g, 2 mmol) and 1-iodopropane (0.27 ml, 2.8 mmol). The mixture was partitioned between ether/H_2O. The organic portion was separated, dried and evaporated to afford the title compound (0.48 g, 99%) as a yellow solid.

NMR ($CDCl_3$) ca 4:1 mixture of rotamers, δ :
0.92 (t, 3H, J=8.4Hz), 1.84 (m, 2H, J=8.4Hz), 2.25 (major, s, 3H), 2.50 (minor, s, 3H), 3.14 (minor, t, 2H, J=8.4Hz), 3.29 (major, t, 2H, J=8.4Hz), 4.02 (t, 2H, J=8.4Hz), 4.09 (major, t, 2H, J=8.4Hz), 4.19 (minor, t, 2H, J=8.4Hz), 6.44 (d, 1H, J=5Hz), 7.02 (d, 1H, J=5Hz), 7.10 (s, 1H), 8.46 (s, 1H).

Description 20

5-n-Propyl-2,3-dihydropyrrolo[2,3-f]indole (D20)

Prepared as in Description 6 using 1-acetyl-5-propyl-2,3-dihydropyrrolo[2,3-f]indole (D19) (0.48g, 1.9 mmol) in ethanol (30 ml) and 10% NaOH solution (5 ml). Chromatography over silica gel eluting with 3% MeOH/CH_2Cl_2 afforded the title compound (0.23g, 60%).

NMR ($CDCl_3$) δ: 0.93 (t, 3H, J=8.4Hz), 1.86 (m, 2H, J=8.4Hz), 3.12 (t, 2H, J=8.4Hz), 3.56 (t, 2H, J=8.4Hz), 4.01 (t, 2H, J=8.4Hz), 6.27 (d, 1H, J=5Hz), 6.87 (s, 1H), 6.97 (d, 1H, J=5Hz), 7.02 (s, 1H).

Description 21

N-(1-Acetyl-5-indolinyl)-2-chloro-N-methylallylamine (D21)

Formaldehyde (40% aq. solution, 2.8 ml, 36 mmol) and 3M sulphuric acid (5ml, 15 mmol) were stirred in ice. To this was added portionwise a suspension of sodium borohydride (1.66g, 44 mmol) and N-(1-acetyl-5-indolinyl)-2-chloroallylamine (D11) (3.08g, 12.2 mmol) in tetrahydrofuran (60 ml), maintaining temperature below 20° C. The mixture was then stirred at ambient temperature for 0.25 h, and basified with excess solid sodium hydroxide. The supernatant was decanted, and the solid residue was dissolved in water (150 ml) and extracted with ethyl acetate. The combined organics were dried (Na_2SO_4) and evaporated to a brown tar, which was dissolved in chloroform, re-dried (Na_2SO_4), filtered and evaporated to give the title compound (3.80g, >100%) as a brown solid. This was used without purification.

NMR ($CDCl_3$) δ: 2.20 (3H, s), 3.00 (3H, s), 3.16 (2H, t, J 7), 3.95-4.20 (4H, m), 5.22 (1H, m), 5.30 (1H, m), 6.56 (2H, m), 8.08 (1H, d, J 8)

Description 22

1-Acetyl-5,6-dimethyl-2,3-dihydropyrrolo[2,3-f]indole and 1-acetyl-6,7-dimethyl-2,3-dihydropyrrolo[3,2-e]indole (D22)

N-(1-Acetyl-5-indolinyl)-2-chloro-N-methylallylamine (D21) (2.1g, 7.9 mmol) was stirred in polyphosphoric acid (44g) at 140° C for 24h, cooled, dispersed in water (200 ml), and extracted with ethyl acetate. The extract was washed with brine, dried (Na_2SO_4) and evaporated to give a pink solid. Chromatography on silica gel, eluting with 0-20% ethyl acetate in dichloromethane, gave:

1) faster-eluting material, the linear [2,3-f]indole (0.21g, 11.6%) as a white solid. NMR showed a mixture of rotamers, in approximate ratio 5:1

NMR ($CDCl_3$) δ: 2.25 (3H, major, s), 2.39 (3H, major, s), 2.41 (3H, minor, s), 2.50 (3H, minor, s), 3.15 (2H, minor, t, J 7), 3.29 (2H, major, t, J 7), 3.62 (3H, major, s), 3.64 (3H, minor, s), 4.10 (2H, major, t, J 7), 4.19 (2H, minor, t, J 7), 6.22 (1H, both, s), 7.03 (1H, major, s), 7.11 (1H, minor, s), 7.21 (1H, minor, s), 8.38 (1H, major, s).

2) slower-eluting material, the angular [3,2-e]indole (0.10g, 5.5%) as a white solid. NMR showed a mixture of rotamers, in approximate ratio 8:1

NMR ($CDCl_3$) δ : 2.25 (3H, major, s), 2.4-2.5 (3H, minor, + 3H, both:m), 3.18 (2H, minor, t, J 8), 3.33 (2H, major, t, J 8), 3.56 (3H, both, s), 4.15 (2H, major, t, J 8), 4.26 (2H, minor, t, J 8), 6.1 (1H, both, m), 7.0-7.15 (1H, both, + 1H, minor: m), 8.20 (1H, major,d,J8).

Description 23

5,6-Dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D23)

This was prepared from 1-acetyl-5,6-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D22) (0.42g, 1.84 mmol), following the procedure of D6. This gave the title compound (0.30g) as a brown gum. NMR indicated ca. 60% conversion to the desired material. This was used without purification.

NMR ($CDCl_3$) δ : 2.36 (3H, s), 3.12 (2H, t, J 7), 3.56 (2H, t, J 7), 3.58 (3H, s), 6.06 (1H, s), 6.78 (1H, s), 7.03 (1H, s).

Description 24

6,7-Dimethyl-2,3-dihydropyrrolo[3,2-e]indole (D24)

This was prepared from 1-acetyl-6,7-dimethyl-2,3-dihydropyrrolo[3,2-e]indole (D22) (0.156g, 0.68 mmol), follwing the procedure of D6. This gave the title compound (0.124g, 97%) as a dark oil.

NMR ($CDCl_3$) δ : 2.38 (3H, s), 3.16 (2H, t, J 7), 3.6 (5H, m), 6.04 (1H, s), 6.63 (1H, d, J 8), 6.95 (1H, d, J 8)

Description 25

N-(6-Quinolyl)trifluoroacetamide (D25)

6-Aminoquinoline (5.75g, 40 mmol) and triethylamine (6.7 ml, 48 mmol) were stirred in chloroform (100 ml), and trifluoroacetic anhydride (6.7 ml, 48 mmol) was added over 2 min. The mixture was stirred for 1 h., when water (100 ml) was added. After stirring for 5 min, the gummy precipitate was filtered off, washed with chloroform and water, and dried *in vacuo* at 50° C. This gave the title compound (7.68g, 80%) as a straw-coloured semi-solid, containing residual triethylamine (NMR).

NMR ($CDCl_3$) δ : 7.57 (1H, dd, J 9, 4), 7.97 (1H, dd, J 9, 2), 8.08 (1H, d, J 9), 8.4 (2H, m), 8.90 (1H, dd, J 5, 2), 11.63 (1H, s).

Description 26

N-(1,2,3,4-Tetrahydro-6-quinolyl)trifluoroacetamide (D26)

N-(6-Quinolyl)trifluoroacetamide (D25) (6.84g, 28.5 mmol) and nickel chloride hexahydrate (1.36g, 5.71 mmol) were stirred in methanol (100 ml), and sodium borohydride (4.3g, 113 mmol) was added portionwise over 0.5h. After stirring for a further 0.5h, another portion of sodium borohydride (1.0g, 26 mmol) was added. After another 0.5 h, the mixture was evaporated to dryness, partitioned between 5M hydrochloric acid (25 ml) and ethyl acetate (100 ml), and stirred until clear. This mixture was neutralised with excess sodium hydrogen carbonate, and separated. The aqueous portion was extracted with further ethyl acetate, and the combined organics were washed with brine, dried (Na_2SO_4) and evaporated. Chromatography on silica gel, eluting with 0-30% ethyl acetate/chloroform, gave the title compound (5.07g, 73%) as a pale greenish solid.

NMR ($CDCl_3$) δ : 1.44 (2H, m), 2.75 (2H, t, J 6), 3.31 (2H, t, J 6), 3.92 (1H, b s), 6.45 (1H, d, J 9), 7.09 (1H, dd, J 9, 2), 7.16 (1H, d, J 2), 7.65 (1H, b s).

Description 27

N-(1-Acetyl-1,2,3,4-tetrahydro-6-quinolyl)trifluoroacetamide (D27)

N-(1,2,3,4-Tetrahydro-6-quinolyl)trifluoroacetamide (D26) (5.64g, 23.1 mmol) and acetyl chloride (2.0 ml, 28 mmol) were stirred in dichloromethane (100 ml) as pyridine (2.25 ml, 28 mmol) was added. The mixture was stirred for 0.5h, when water (100 ml) was added. After vigorous stirring for 0.25 h, it was acidified with 5M hydrochloric acid, and separated. The organic portion was washed with brine, dried (Na_2SO_4), and evaporated, giving the title compound (5.24 g, 79%) as a cream solid.

NMR ($CDCl_3$) δ : 1.99 (2H, m), 2.25 (3H, s), 2.57 (2H, t, J 6), 3.78 (2H, t, J 6), 7.3 (b), 7.52 (1H, b s), 8.08 (1H, b s).

Description 28

1-Acetyl-6-amino-1,2,3,4-tetrahydroquinoline (D28)

N-(1-Acetyl-1,2,3,4-tetrahydro-6-quinolyl)trifluoroacetamide (D27) (1.85g, 6.5 mmol) was stirred in ethanol (15 ml), and sodium hydroxide (0.52g, 13.0 mmol) was added in water (3ml). The mixture was stirred at ambient temperature for 0.5 h, and then heated to reflux over 0.25 h. After 0.5 h at reflux, the mixture was cooled, acidified with 5M hydrochloric acid, basified with solid sodium carbonate, diluted with water (100 ml), and

extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to give the title compound (1.38g, >100%) as a brown oil containing residual chloroform (NMR).

NMR ($CDCl_3$) δ : 1.92 (2H, m), 2.27 (3H, s), 2.60 (2H, m), 3.67 (2H, b s), 3.79 (2H, b m), 6.5 (2H, m), 6.87 (1H, b d, J 6).

Description 29

1-Acetyl-6-(2,2-diethoxyethyl)amino-1,2,3,4-tetrahydroquinoline (D29)

1-Acetyl-6-amino-1,2,3,4-tetrahydroquinoline (D28) (2.35g, 12.4 mmol) and N,N-diisopropylethylamine (2.7 ml, 15.5 mmol) were stirred in 1,2-dichloroethane (50 ml) under Ar. 2,2-Diethoxyethyl trifluoromethanesulphonate (3.78g, ca. 90% purity, ca 13 mmol) was added dropwise in 1,2-dichloroethane (10 ml) over 5 min. The mixture was then stirred at reflux for 0.5 h, cooled, washed with water, dried (Na_2SO_4) and evaporated to give a black oil. This material was combined with that obtained by an identical procedure using 1.40g of the aminoquinoline reagent, and chromatographed on silica gel using 0-100% ethyl acetate/chloroform. This gave the title compound (3.72g, 61%) as an amber oil, contaminated with a little dialkylated material (NMR).

NMR ($CDCl_3$) δ : 1.25 (6H, t, J 7), 1.92 (2H, m), 2.20 (3H, s), 2.63 (2H, b m), 3.25 (2H, t, J 5), 3.5-3.9 (7H, m), 4.69 (1H, t, J 6), 6.45 (2H, m), 6.89 (1H, b d, J 6)

Description 30

5-Acetyl-1-trifluoroacetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D30)

1-Acetyl-6-(2,2-diethoxyethyl)amino-1,2,3,4-tetrahydroquinoline (D29) (3.72g, 12.2 mmol) was stirred at 0° C under Ar in a mixture of trifluoroacetic acid (20 ml) and trifluoroacetic anhydride (20 ml) for 0.5 h. Further trifluoroacetic acid (30 ml) was added, and the solution was then stirred at reflux for 90 h, cooled, and evaporated to give a black gum. Chromatography on silica gel, eluting with 0-60% ethyl acetate/chloroform, gave the title compound (2.77g, 73%) as an amber oil.

NMR ($CDCl_3/D_6$-DMSO) δ : 2.03 (2H, m), 2.25 (3H, s), 2.87 (2H, t, J 6), 3.80 (2H, t, J 7), 6.83 (1H, d, J 4), 7.51 (2H, m), 8.25 (1H, s)

Description 31

5-Acetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D31)

5-Acetyl-1-trifluoroacetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D30) (2.76g, 8.9 mmol) and anhydrous potassium carbonate (3.7g, 27 mmol) were stirred in methanol (50 ml) for 1 h. The mixture was then concentrated *in vacuo*, diluted with water (100 ml), and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, giving the title compound (1.40g, 73%) as an orange-brown solid. NMR showed a mixture of rotamers in approximate ratio 9:1.

NMR ($CDCl_3$) δ : 1.97 (2H, major, m), 2.07 (2H, minor, m), 2.22 (3H, both, s), 2.73 (2H, major, t, J 6), 3.01 (2H, minor, t, J 6), 3.86 (2H, both, t, J 7), 6.52 (1H, both, m), 7.20 (2H, both, m), 7.34 (1H, major, s), 8.33 (1H, both, b).

Description 32

5-Acetyl-1-methyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D32)

5-Acetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D31) (1.39g, 6.5 mmol) in dry dimethylformamide (DMF) (20ml) was added, with stirring under Ar, to a suspension of sodium hydride (80% in mineral oil, 0.25g, 8.3 mmol) in DMF (5ml). After stirring for 20 min, iodomethane (0.61 ml, 9.8 mmol) was added. The resulting suspension was stirred for 1h, diluted with water (100 ml), and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4) and evaporated to give a gum. Chromatography on silica gel, eluting with 0-100% ethyl acetate/chloroform, gave the title compound (0.97g, 65%) as a pale, straw coloured oil which solidified on standing. NMR showed a mixture of rotamers in approximate ratio 6:1.

NMR ($CDCl_3$) δ : 1.97 (2H, both, m), 2.20 (3H, both, s), 2.75 (2H, major, t, J 6), 2.98 (2H, minor, t, J 6), 3.78 (3H, both, s), 3.84 (2H, both, t, J 7), 6.45 (1H, both, d, J 3), 7.04 (1H, both, d, J 3), 7.12 (1H, both, s), 7.31 (1H, both, s).

Description 33

1-Methyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D33)

5-Acetyl-1-methyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D32) (0.96g, 4.2 mmol) was dissolved in ethanol (10 ml), and 2.5 M sodium hydroxide (90 ml) was added. This mixture was stirred at reflux under Ar for 23h, cooled, diluted with water (200 ml), and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated to give the title compound (0.64g, 81%) as a light brown gum.

NMR ($CDCl_3$) δ : 2.00 (2H, m), 2.95 (2H, t, J 6), 3.0 (1H, b), 3.30 (2H, t, J 5.5), 3.68 (3H, s), 6.20 (1H, d, J 3), 6.72 (1H, s), 6.87 (1H, d, J 3), 6.92 (1H, s).

Description 34

3-(1-Methyl-5-nitro-4-indolyl)propionitrile (D34)

2-(1-Methyl-5-nitro-4-indolyl)ethane methanesulphonate (D9) (1.60g, 5.4 mmol) and sodium cyanide (0.53g, 10.8 mmol) were stirred in dry dimethyl sulphoxide (15 ml) at 100° C under Ar for 5h. After cooling, the mixture was diluted with ethyl acetate (150 ml), washed with water, dried (Na_2SO_4) and evaporated to give the title compound (1.16g, 94%) as a brown solid.

NMR ($CDCl_3$) δ : 2.93 (2H, t, J 7), 3.60 (2H, t, J 7), 3.87 (3H, s), 6.80 (1H, d, J 3), 7.3 (2H, m), 8.05 (1H, d, J 8).

Description 35

3-(1-Methyl-5-nitro-4-indolyl)propanoic acid (D35)

3-(1-Methyl-5-nitro-4-indolyl)propionitrile (D34) (1.16g, 5.1 mmol) was stirred at reflux in concentrated hydrochloric acid (150 ml) for 7.5 h, After cooling, the dark mixture was extracted with ethyl acetate; the extract was dried (Na_2SO_4) and evaporated to give the title compound (0.74 g, 59%) as a brown solid.

NMR ($CDCl_3$) δ : 2.88 (2H, t, J 7), 3.55 (2H, t, J 7), 3.84 (3H, s), 6.76 (1H, d, J 3), 7.21 (1H, d, J 3), 7.25 (1H, d, J 8), 7.98 (1H, d, J 8).

Description 36

Methyl 3-(1-methyl-5-nitro-4-indolyl)propanoate (D36)

3-(1-Methyl-5-nitro-4-indolyl)propanoic acid (D35) (0.94g, 3.8 mmol) was stirred in methanol (10 ml) as thionyl chloride (1 ml) was added dropwise. The mixture was then stirred at reflux for 2h, and evaporated to a dark oil. Chromatography on silica gel, eluting with dichloromethane, gave the title compound (0.58g, 58%) as a pale yellow solid.

NMR ($CDCl_3$) δ : 2.81 (2H, t, J 7), 3.55 (2H, t, J 7), 3.70 (3H, s), 3.84 (3H, s), 6.73 (1H, d, J 3), 7.20 (1H, d, J 3), 7.24 (1H, d, J 8), 7.97 (1H, d, J 8).

Description 37

3-(1-Methyl-5-nitro-4-indolyl)-1-propanol (D37)

Methyl 3-(1-methyl-5-nitro-4-indolyl)propanoate (D36) (0.46g, 1.8 mmol) was stirred under Ar in tetrahydrofuran (25 ml) as lithium aluminium hydride (0.10g, 2.6 mmol) was added portionwise. After 3h, water (0.5 ml), 2.5M sodium hydroxide solution (0.75 ml) and water (1.5 ml) were successively added. The mixture was then dried (Na_2SO_4) and evaporated to a brown oil. Chromatography on silica gel, eluting with 0-20% ethyl acetate in dichloromethane, then gave the title compound (0.39g, 95%) as an orange solid.

NMR ($CDCl_3$) δ : 2.05 (2H, m), 3.34 (2H, t, J 7), 3.78 (2H, q, J 6), 3.85 (4H, m), 6.77 (1H, d, J 3), 7.18 (1H, d, J 3), 7.22 (1H, d, J 8), 7.96 (1H, d, J 8)

Description 38

3-(1-Methyl-5-nitro-4-indolyl)-1-propyl methanesulphonate (D38)

This was prepared from 3-(1-methyl-5-nitro-4-indolyl)-1-propanol (D37) (0.39g, 1.7 mmol), following the procedure of Description 8. This gave the title compound (0.54g, >100%) as a brown oil, which was used without purification.

NMR ($CDCl_3$) δ : 2.25 (2H, m), 3.05 (3H, s), 3.36 (2H, t, J 7), 3.84 (3H, s), 4.37 (2H, t, J 7), 6.73 (1H, d, J 3), 7.21 (1H, d, J 3), 7.25 (1H, d, J 8), 7.98 (1H, d, J 8).

Description 39

3-Methyl-6,7,8,9-tetrahydro-3H-pyrrolo[3,2-f]quinoline (D39)

This was prepared from 3-(1-methyl-5-nitro-4-indolyl)-1-propyl methanesulphonate (D38) (0.54g, 1.7 mmol), following the procedure of Description 10. Neutralisation with sodium hydrogen carbonate solution gave the title compound (0.21g, 65%), as a brown oil.

NMR ($CDCl_3$) δ : 2.05 (2H, m), 2.95 (2H, t, J 6), 3.32 (2H, t, J 6), 3.63 (1H, b), 3.73 (3H, s), 6.70 (1H, d, J 3), 6.86 (1H, d, J 8), 6.96 (1H, d, J 3), 7.00 (1H, d, J 8)

Description 40

6-Methyl-8-(N,N-dimethylaminomethyl)-3-(3-pyridyl-carbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (D40)

6-Methyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo [3,2-e]indole (E2) (0.65g, 0.0022moles) suspended in 1,4-dioxan (10ml) was added to a mixture of 37% aqueous

formaldehyde (0.2ml) and 33% dimethylamine in ethanol (0.46ml) in a mixture of 1,4-dioxan (3.5ml) and glacial acetic acid (3.5ml) at 5°C with stirring. The mixture was stirred at ambient temperature for 20hrs then diluted with water (80ml) and basified with 10% aqueous sodium hydroxide. Filtration gave the title compound (D40) (0.66g, 85%) as an off white solid.

NMR (D_6-DMSO) δ: 2.17 (6H,s), 3.41 (2H, s), 3.50 (2H, t, J=8Hz), 3.71 (3H, s), 4.19 (2H, t, J=8Hz). 7.11-7.17 (1H, m), 7.26-7.34 (1H, m), 7.88 (1H, d, J=8Hz), 7.95-8.01 (1H, m), 8.16-8.22 (1H, m), 8.58 (1H, s), 8.74 (1H, d, J=4Hz)

Description 41

2,3-Dihydro-1-(1-imidazolylcarbonyl)-5-methyl-1H-pyrrolo[2,3-f]indole (D41)

To a solution of carbonyldimidazole (0.71g, 4.4mmol) in DMF (25ml) was added dihydropyrroloindole (D6) (0.69g, 4mmol) in DMF (5ml). The mixture was stirred for 1h at 110-140°C, then cooled and poured into water. After allowing the precipitate to form, solid material was filtered off, washed with water and dried. Crude product was recrystallised from dichloromethane/petrol to give the title compound (0.45g, 42%), m.p. 178-180°C.

NMR (D_6-DMSO) δ: 3.22 (2H, t, J=8), 3.77 (3H, s), 4.24 (3H, t, J=8), 6.40 (1H, d, J=4), 7.08 (1H, s), 7.28 (1H, d, J=4), 7.38 (1H, s), 7.69 (1H, s), 7.83 (1H, broad s), 8.24 (1H, s).

Description 42

1-Acetyl-2-methyl indoline (D42)

2-methylindoline (5.0g, 0.037 mol) in acetic anhydride (40 ml) and pyridine (2 ml) was heated under argon at reflux for 4 h. The mixture was cooled, poured into water (100 ml), allowed to stand for 30 mins, extracted (EtOAc 2x 250 ml), the combined organic solution washed (K_2CO_3 solution), and dried (Na_2SO_4). The solution was filtered, evaporated to dryness under reduced pressure and purified by column chromatography (SiO_2, Et_2O) to afford the product as a yellow oil (6.57 g, 96%) which crystallised on standing.

NMR ($CDCl_3$) δ : 1.30 (3H, d), 2.30 (3H, s), 2.68 (1H, d), 3.41 (1H, dd), 4.49 (1H, m), 7.04 (1H, t), 7.24 (2H, m), 8.18 (1H, d).

Description 43

1-Acetyl-2-methyl-5-nitroindoline (D43)

1-Acetyl-2-methylindoline (D42) (6.57g, 37.5 mmol) was dissolved in AcOH (56 ml) and a mixture of conc. HNO_3 (16 ml) and AcOH (8 ml) was added. The blue solution was heated to 50° C under Ar, whereupon the solution was red/brown and began to emit brown fumes. After stirring for 2h at 50° C, the solution was poured into water (500 ml), extracted with EtOAc (300 ml), washed with sat. aq. K_2CO_3 solution (200 ml), dried (Na_2SO_4), evaporated under reduced pressure to give an orange oil. This was purified by column chromatography (SiO_2) to afford an orange oil (7.82g, 95%) which solidified on standing.

NMR ($CDCl_3$) δ :
1.3 (3H, d), 2.30 (3H, s), 2.72 (1H, d), 3.41 (1H, dd), 4.58 (1H, m), 8.10 (3H, m).

Description 44

1-Acetyl-5-amino-2-methylindoline (D44)

1-Acetyl-2-methyl-5-nitroindoline (D43), (16g, 0.073 mol) was dissolved in EtOH (180 ml), 10% Pd-C (0.3g) added and the suspension hydrogenated at 50° C and 50 psi on a Parr rocker hydrogenator for 6 h. The mixture was filtered through celite and evaporated to dryness to afford the product (D44) (14.0g, 100%) as a red oil.

NMR ($CDCl_3$) δ : 1.30 (3H, d), 2.24 (3H, s), 2.58 (1H, d), 3.38 (1H, dd), 4.41 (1H, m), 6.58 (2H, m), 7.98 (1H, d).

Description 45

1-Acetyl-5-[(2,2-dimethoxyethyl)-amino]-2-methylindoline (D45)

1-Acetyl-5-amino-2-methylindoline (D44), (5.0g, 0.027 mol) was dissolved in EtOH (100 ml), 10% Pd-C (0.5g) added followed by glycolaldehyde dimethyl acetal (5.53g of a 60% solution in water, 1.2 equiv.) The mixture was hydrogenated at rtp with stirring overnight, filtered through celite, evaporated to near dryness, taken up in EtOAc (200 ml), washed (H_2O, brine), dried (Na_2SO_4), and evaporated to dryness under reduced pressure to afford the product (D45) as a brown oil (7.69g, 95%).

NMR ($CDCl_3$) δ : 1.30 (3H, d), 2.24 (3H, s), 2.58 (1H, d), 3.23 (2H, d), 3.33 (1H, dd), 3.41 (6H, s), 4.41 (1H, m), 4.58 (1H, t), 6.51 (2H, m), 7.98 (1H, d).

Description 46

1-Acetyl-2-methyl-2,3-dihydropyrrolo-[2,3-f]-indole (D46)

1-Acetyl-5-[(2,2-dimethoxyethyl)amino}-2-methylindoline (D45) (7.5g, 0.027 mol) was dissolved in TFA (32 ml) and cooled to 0° C under Ar. TFAA (30 ml) was added and the brown solution stirred at 0° C for 30 mins. TFA (50 ml) was added and the mixture heated at reflux for 6 days, evaporated to dryness and purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 0.5-0.75%) to afford the product as a pale pink solid (4.84 g, 58%). 2.84 g, (9.2 mmol) was dissolved in MeOH (70 ml) and anhydrous K_2CO_3 (1.90 g, 1.5 equiv.) added. The mixture was stirred vigorously for 1h, heated briefly to 40° C, cooled, evaporated to dryness and partitioned between water and $CHCl_3$. The organic layer was dried (Na_2SO_4) and evaporated to dryness under reduced pressure to afford the product (D46) (1.89g, 96%) as a pale brown solid.

NMR ($CDCl_3$) δ : 0.72 (3H, d), 2.17 (1H, d), 2.52 (3H, s), 2.91 (1H, m), 3.98 (1H, m), 5.80 (1H, s), 6.58 (1H, s), 6.68 (1H, s), 7.70 (1H, s), 9.95 (1H, s, N-H)

Description 47

2-Methyl-2,3-dihydropyrrolo[2,3-f]indole (D47)

1-Acetyl-2-methyl-2,3-dihydropyrrolo [2,3-f] indole (D46) (2.55g, 0.0119 mol) in EtOH (30 ml) and 10% NaOH (120 ml) was heated at reflux under Ar overnight. The mixture was extracted with EtOAc (2 x 200 ml) the organic solution dried (Na_2SO_4), evaporated to dryness and purified by column chromatography (SiO_2, Et_2O/MeOH 1%) to afford the product (D47) (1.4g, 68%).

NMR ($CDCl_3$) δ : 1.32 (3H, d), 2.71 (1H, dd), 3.19 (1H, dd), 3.98 (1H, m), 6.38 (1H, s), 6.83 (1H, s), 7.07 (1H, s), 7.12 (1H, s), 7.92 (1H, bs, NH)

Description 48

1-Acetyl-2,5-dimethyl-2,3-dihydro-pyrrolo[2,3-f]indole (D48)

As for Description 5 using 1-acetyl-2-methyl-2,3-dihydropyrrolo[2,3-f]indole (D46) (1.35g, 6.3 mmol) in dry DMF (10 ml), NaH (265 mg of 80% suspension in oil) in DMF (10 ml) and MeI (0.55 ml, 1.4 equiv.). After the reaction was complete, the mixture was evaporated to dryness, partitioned between sat aq K_2CO_3 (100 ml) and CH_2Cl_2 (3 x 100 ml), the organic solutions dried, combined and evaporated to dryness with subsequent purification by column chromatography (SiO_2, Et_2O/MeOH 2-20%) to afford the product (D48) as a pale yellow solid (1.16g, 81%).

NMR ($CDCl_3$) δ : 1.30 (3H, d), 2.32 (3H, s), 2.40 (1H, d), 2.75 (1H, dd), 3.76 (3H, s, NMe), 4.50 (1H, m), 6.47 (1H, s), 7.00 (1H, s), 7.12 (1H, s), 8.41 (1H, s).

Description 49

2,5 Dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D49)

1-Acetyl-2,5-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D48) (1.1g, 4.82 mmol) in EtOH (40 ml) and 10% NaOH (3.45 ml, 1.8 eq) with solid NaOH (1.93, 10 eq) was heated at reflux under an Ar atmosphere (Firestone valve) for 6 h, partitioned between H_2O and CH_2Cl_2, the organic solutions dried (Na_2SO_4), evaporated to dryness and purified by column chromatography (SiO_2, $CHCl_3$/MeOH 10%) to afford the product as an oil (370 mg, 37%).

NMR ($CDCl_3$) δ : 1.30 (3H, d), 2.72 (1H, dd), 3.22 (1H, dd), 3.78 (3H, s, NMe), 4.00 (1H, m), 6.28 (1H, d), 6.89 (1H, d), 6.80 (1H, s), 7.08 (1H, s).

Example 1

5-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E1)

Nicotinoyl azide (0.56g, 3.8 mmol) was stirred at reflux under nitrogen in dry toluene (20 ml) for 0.75h, and cooled to ambient temperature. 5-Methyl-2,3-dihydropyrrolo[2,3-f]indole (D6) (0.59g, nominally 3.4 mmol) was added in dichloromethane (20 ml) was stirring, with immediate precipitation. The suspension was stirred for 2.5h, and the solid was then filtered off, washed with 1:1 dichloromethane/toluene, and thoroughly dried. This gave the title compound (0.60g, 60%) as a light grey powder.

NMR (D_6-DMSO) δ: 3.28 (2H, t, J 8), 3.73 (3H, s), 4.17 (2H, t, J 8), 6.81 (1H, d, J 3), 7.1-7.35 (3H, m), 8.0 (1H, m), 8.03 (1H, s), 8.21 (1H, m), 8.63 (1H, s), 8.76 (1H, d, J 2).

Found: C, 70.1; H, 5.6; N, 18.8%
$C_{17}H_{16}N_4O$ requires C, 69.8; H, 5.5; N, 19.2%
Found: M^+ 292, $C_{17}H_{16}N_4O$ requires 292

Example 2

6-Methyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (E2)

2-(1-Methyl-5-nitro-4-indolyl)ethyl methanesulphonate (D9) (0.38g, 1.3 mmol) was hydrogenated over 5% palladium on charcoal (0.23g) in dry DMF (20 ml) at 80 p.s.i. H_2 for 2h, diluted with ethanol (80 ml), filtered through Kieselguhr, and evaporated to a brown gum. This was dissolved in dichloromethane (10 ml), and reacted with 3-pyridyl isocyanate, formed from pyrolysis of nicotinoyl azide (0.20g, 2.35 mmol) as described in Example 1, but adding triethylamine (0.18g, 1.3 mmol) to the isocyanate before addition of the crude mesylate salt. After a reaction time of 16h, filtration, washing, and drying as before, gave the title compound (0.16g, 44%) as a light green powder.

NMR (D_6-DMSO) δ: 3.33 (2H, t, J 8), 3.77 (3H, s), 4.22 (2H, t, J 8), 6.28 (1H, d, J 3), 7.23 (1H, d, J 8), 7.3 (2H, m), 7.89 (1H, d, J 8), 8.0 (1H, d, J 8), 8.2 (1H, d, J 5), 8.61 (1H, s), 8.75 (1H, d, J 2).

Found: C, 66.1; H, 5.4; N, 17.8%
$C_{17}H_{16}N_4O$. H_2O requires C, 65.8; H, 5.8; N, 18.0%
Found: M^+ 292, $C_{17}H_{16}N_4O$ requires 292

Example 3

5,7-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E3)

This was prepared from 5,7-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D16) (0.30g, nominally 1.6 mmol) following the procedure of Example 1. This gave the title compound (0.19g, 42% from (D15)) as a white solid, still containing traces of toluene (NMR).

NMR (D_6-DMSO) δ: 2.19 (3H, s), 3.27 (2H, t, J 8), 3.67 (3H, s), 4.18 (2H, t, J 8), 6.96 (1H, s), 7.21 (1H, s), 7.32 (1H, dd, J 7, 4), 8.00 (1H, s), 8.02 (1H, dd, J 7, 2), 8.22 (1H, dd, J 4, 2), 8.62 (1H, s), 8.77 (1H, s).

Found: C, 70.6; H, 6.0%, $C_{18}H_{18}N_4O$ requires C, 70.6; H, 5.9%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 4

1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E4)

This material was isolated by chromatography on silica gel, eluting with 0-5% methanol in chloroform, as an impurity in a sample of 5-methyl-1-(3-pyridylcarbamoyl)-2,3-

dihydropyrrolo[2,3-f]indole (E1). Recrystallisation from ethanol/petroleum ether (b.p. 60-80° C) gave the compound as fine grey needles, m.p. 207-8° C (dec.), still containing ethanol of crystallisation. It can also be prepared by hydrolysing D4 and then coupling with 3-pyridylisocyanate.

NMR (D_6-DMSO) δ : 1.15 (t, J 7; EtOH), 3.34 (2H, t, J 8), 3.55 (quintet, J 7; EtOH), 4.26 (2H, t, J 8), 4.48 (t, J 6; EtOH), 6.42 (1H, s), 7.31 (2H, s), 7.42 (1H, dd, J 7, 4), 8.05-8.2 (2H, m), 8.31 (1H, d, J 4), 8.72 (1H, s) 8.86 (1H, s), 10.95 (1H, s)

Found: C, 67.2; H, 6.1; N, 17.6%
$C_{16}H_{14}N_4O$. 0.75(C_2H_6O) requires C, 67.2; H, 6.0; N, 17.9%
Found: M^+ 278, $C_{16}H_{14}N_4O$ requires 278

Example 5

6-Methyl-3-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (E5)

The title compound was prepared from 4-aminopyridine, 1,1'-carbonyldiimidazole, 6-methyl-(2,3-dihydropyrrolo[3,2-e]indole) hydrochloride (D10) and triethylamine in methylene chloride/dimethylformamide. The reaction mixture was poured onto water to afford the title compound in 98% yield, m.p >230° C.

NMR (D_6-DMSO) δ : 3.30 (2H, t, J 7), 3.75 (3H, s), 4.25 (2H, t, J 7), 6.30 (1H, d, J 4), 7.21 (1H, d, J 10), 7.30 (1H, d, J 4), 7.58 (1H, s), 7.62 (1H, s), 7.90 (1H, d, J 10), 8.31 (1H, s), 8.36 (1H, s), 8.75 (1H, s).

Found: C, 69.5; H, 5.6; N, 19.1%, $C_{17}H_{16}N_4O$ requires C, 69.8; H, 5.5; N, 19.1%
Found M^+ 292, $C_{17}H_{16}N_4O$ requires 292.

Example 6

6-Methyl-3-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (E6)

The title compound was prepared from 2-aminopyridine, 1,1'-carbonyldiimidazole, 6-methyl-(2,3-dihydropyrrolo[3,2-e]indole) hydrochloride (D10) and triethylamine using a procedure similar to that described for Example 5, in 39% yield, m.p 143-4° C.

NMR (D_6-DMSO) δ : 3.35 (2H, t, J 7), 3.85 (3H, s), 4.38 (2H, t, J 7), 6.40 (1H, d, J 4), 7.08-7.15 (1H, m), 7.33 (1H, d, J 7), 7.41 (1H, d, J 4), 7.79-7.89 (1H, m), 7.95-8.05 (2H, m), 8.39 (1H, d, J 4), 9.00 (1H, s).

Found: C, 69.6; H, 5.6; N, 19.1%, $C_{17}H_{16}N_4O$ requires C, 69.8, H, 5.5; N, 19.2%
Found M^+ 292, $C_{17}H_{16}N_4O$ requires 292

Example 7

5-Methyl-1-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E7)

The title compound was prepared from 2-aminopyridine, 1,1'-carbonyldiimidazole and 5-methyl-(2,3-dihydropyrrolo[2,3-f]indole) (D7) using a procedure similar to that described for Example 5, in 75% yield, m.p 137-8° C.

NMR (D_6-DMSO) δ : 3.25 (2H, t, J 7), 3.75 (3H, s), 4.21 (2H, t, J 7), 6.31 (1H, d, J4), 7.03 (1H, t, J 4), 7.20 (1H, s), 7.30 (1H, s), 7.75 (1H, t, J 7), 7.95 (1H, d, J 7), 8.04 (1H, s), 8.30 (1H, d, J 4), 8.95 (1H, s).

Found: C, 66.0; H, 5.6; N, 18.0%, $C_{17}H_{16}N_4O$. H_2O requires C,65.8; H,5.8; N,18.0%
Found: M^+ 292, $C_{17}H_{16}N_4O$ requires 292

Example 8

5-Methyl-1-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E8)

The title compound was prepared from 4-aminopyridine, 1,1'-carbonyldiimidazole and 5-methyl-(2,3-dihydropyrrolo[2,3-f]indole) (D7) using a procedure similar to that described for Example 5, in 84% yield, m.p 251-3° C.

NMR (D_6-DMSO) δ : 3.25 (2H, t, J 7), 3.72 (3H, s), 4.18 (2H, t, J 7), 6.32 (1H, d, J 4), 7.18 (1H, d, J 4), 7.27 (1H, s), 7.62 (2H, d, J 7), 8.05 (1H, s), 8.35 (2H, d, J 7), 8.85 (1H, s).

Found: C, 69.2; H, 5.7; N, 19.0%, $C_{17}H_{16}N_4O$ requires C, 69.8; H, 5.5; N, 19.2%
Found: M^+ 292, $C_{17}H_{16}N_4O$ requires 292

Example 9

5-Methyl-1-(3-pyridylcarbamoyl)-2,3,6,7-tetrahydropyrrolo[2,3-f]indole (E9)

5-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E1) (0.8g, 2.7 mmol) was treated with sodium cyanoborohydride (0.86g, 13.7 mmol) in glacial acetic acid (20 ml) at room temperature for 4h. Water (100 ml) was added and the mixture basified with 10% aqueous sodium hydroxide. Extraction with dichloromethane followed by drying

(Na_2SO_4) and evaporation to dryness gave a solid. Recrystallisation from methanol/60-80 petrol gave the title compound (E9) (0.43g, 53%) as a white crystalline solid, m.p. 153-155° C.

NMR (D_6-DMSO) δ : 2.62 (3H, s), 2.80 (2H, t, J 8), 3.05 (2H, t, J 8), 3.17 (2H, t, J 8), 4.10 (2H, t, J 8), 6.40 (1H, s), 7.30 (1H, q, J 4), 7.65 (1H, s), 7.91-7.98 (1H, m), 8.19 (1H, d, J 4), 8.55 (1H, s), 8.72 (1H, d, J 4)

Found: C, 68.7; H, 6.2; N, 18.9%, $C_{17}H_{18}N_4O$ requires C, 69.4; H, 6.2; N, 19.0%
Found: M^+ 294, $C_{17}H_{18}N_4O$ requires 294

Example 10

5-Ethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E10)

The title compound was prepared from 5-ethyl-2,3-dihydropyrrolo[2,3-f]indole (D18) and 3-pyridylisocyanate (prepared *in situ* from nicotinoyl azide) in 58% yield using a procedure similar to that for E1, m.p. 202-203° C.

NMR (D_6DMSO) δ : 1.33 (3H, t, J 8), 3.28 (2H, t, J 10), 4.16 (4H, m), 6.31 (1H, d, J 3), 7.24 (1H, d, J 3), 7.30 (1H, s), 7.32 (1H, m), 8.00 (1H, m), 8.03 (1H, s), 8.22 (1H, m), 8.65 (1H, s), 8.77 (1H, s).

Found: C, 70.70; H, 6.01; N, 18.46%, $C_{18}H_{18}N_4O$ requires C, 70.57; H, 5.92; N, 18.29%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 11

5-n-Propyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E11)

Prepared as in Example 1 using nicotinoyl azide (0.19g, 1.4 mmol) and 5-propyl-2,3-dihydropyrrolo[2,3-f]indole (0.23g, 1.2 mol). Chromatography over silica gel eluting with 5% MeOH/CH_2Cl_2 afforded the title compound (0.27g, 70%) as a pale green powder.

NMR ($CDCl_3$) δ: 0.93 (t, 3H, J=8.4Hz), 1.87 (m, 2H, J=8.4Hz), 3.31 (t, 2H, J=8.4Hz), 4.05 (t, 2H, J=8.4Hz), 4.28 (t, 2H, J=8.4Hz), 6.45 (d, 1H, J=2.8Hz), 6.77 (br s, 1H), 7.06 (d, 1H, J=2.8Hz), 7.18 (s, 1H), 7.29 (m, 1H,), 7.92 (s, 1H), 7.85 (m, 1H), 8.30 (dd, 1H, J=2.8Hz), 8.51 (s, 1H)

Found: C; 70.54 H; 6.34 N; 17.39
$C_{19}H_{20}N_4O.^1/_8H_2O$ requires C; 70.58, H; 6.39, N; 17.33
Found: $M^+ = 320$. $C_{19}H_{20}N_4O$ requires 320

Example 12

5,6-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E12)

This was prepared from 5,6-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D23) (0.30g, nominally 1.61 mmol), following the procedure of Example 1. This gave the title compound (0.219g, 39% from D22), as a buff powder, containing residual CH_2Cl_2 (NMR), and which decomposed at ca. 225° C.

NMR (D_6-DMSO) δ : 2.36 (3H, s), 3.26 (2H, t, J 8), 3.60 (3H, s), 4.17 (2H, t, J 8), 6.11 (1H, s), 7.21 (1H, s), 7.32 (1H, dd, J 7, 4), 7.93 (1H, s), 8.00 (1H, d, J 7), 8.21 (1H, d, J 4), 8.63 (1H, s), 8.75 (1H, d, J 2).

Found: C, 69.2; H, 5.9; N, 17.6%
$C_{18}H_{18}N_4O.(0.08\ CH_2Cl_2)$ requires C, 69.3; H, 5.8; N, 17.9%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 13

6,7-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (E13)

This was prepared from 6,7-dimethyl-2,3-dihydropyrrolo[3,2-e]indole (D24) (0.124g, 0.67 mmol), following the procedure of Example 1. This gave the title compound (0.128g, 62%), as a light brown powder, containing residual CH_2Cl_2 (NMR), m.p. 216-8° C (decomp).

NMR (D_6-DMSO) δ : 2.45 (3H, s), 3.33 (2H, t, J 8), 3.70 (3H, s), 4.28 (2H, t, J 8), 6.15 (1H, s), 7.21 (1H, d, J 9), 7.37 (1H, dd, J 8, 5), 7.86 (1H, d, J 9), 8.06 (1H, dm, J 9), 8.26 (1H, d, J 5), 8.67 (1H, s), 8.81 (1H, d, J 2).

Found: C, 69.4; H, 5.9; N, 17.7%
$C_{18}H_{18}N_4O.(0.08\ CH_2Cl_2)$ requires C, 69.3; H, 5.8; N, 17.9%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 14

1-Methyl-N-(3-pyridyl)-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline-5-carboxamide (E14)

This material was prepared from 1-methyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D33) (0.64g, 3.4 mmol), following the procedure of Example 1. This gave a pale orange solid, 0.64g (60%). Recrystallisation from ethanol/petroleum ether (b.p. 60-80° C) gave lustrous pale orange flakes (0.56g), m.p. 154.5-155.5° C.

NMR (D_6-DMSO) δ : 1.93 (2H, m), 2.80 (2H, t, J 7), 3.72 (2H, t, J 7), 3.77 (3H, s), 6.34 (1H, d, J 3), 7.25 (3H, m), 7.49 (1H, s), 7.89 (1H, dt, J 8, 2), 8.15 (1H, dd, J 4, 2), 8.65 (2H, m).

Found: C, 70.2; H, 5.4; N, 18.0%, $C_{18}H_{18}N_4O$ requires C, 70.6; H, 5.9; N, 18.3%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 15

3-Methyl-N-(3-pyridyl)-6,7,8,9-tetrahydro-3H-pyrrolo[3,2-f]quinoline-6-carboxamide (E15)

This was prepared from 3-methyl-6,7,8,9-tetrahydro-3H-pyrrolo[3,2-f]quinoline (D39) (0.21g, 1.1 mmol), following the procedure of Example 1. The reaction was worked up by evaporation to give a brown oil, which was chromatographed on silica gel, eluting with 0-10% methanol/dichloromethane. Finally, recrystallisation from ethanol/petroleum ether (b.p. 60-80°C) gave the title compound (0.26g, 75%) as a cream solid, m.p. 174-5° C, containing residual ethanol (NMR)

NMR (D_6-DMSO) δ : 1.98 (2H, m), 2.94 (2H, t, J 7), 3.75 (5H, m), 6.41 (1H, d, J 3), 7.13 (1H, d, J 8), 7.23 (1H, d, J 8), 7.25-7.30 (2H, m), 7.89 (1H, m), 8.15 (1H, d, J 3), 8.64 (1H, m) 8.77 (1H, s)

Found: C, 70.2; H, 6.1; N, 17.8%
$C_{18}H_{18}N_4O$. (0.14 C_2H_6O) requires C, 70.2; H, 6.1; N, 17.9%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306.

Example 16

6-Methyl-3-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole (E16)

The title compound was prepared from 2-methyl-4-aminoquinoline, 1,1'-carbonyl diimidazole, 6-methyl-(2,3-dihydropyrrolo-[3,2-e]indole)hydrochloride (D10) and triethylamine, in 76% yield, m.p. > 230° C.

NMR (D_6-DMSO)δ: 2.60 (3H, s), 3.34 (2H, t, J 7), 3.75 (3H, s), 4.42 (2H, t, J 7), 6.31 (1H, d, J 3), 7.25 (1H, d, J 8), 7.35 (1H, d, J 3), 7.52 (1H, t, J 7), 7.70 (1H, t, J 7), 7.80 (1H, s), 7.88 (1H, s), 7.92 (1H, s), 8.17 (1H, d, J 7), 8.70 (1H, s)

Found: C, 73.3; H, 5.8; N, 15.5
$C_{22}H_{20}N_4O.{}^1/_4 H_2O$ requires C, 73.3; H, 5.7; N, 15.5
Found: M^+ 356, $C_{22}H_{20}N_4O$ requires 356

Example 17

6-Methyl-3-(5-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole (E17)

The title compound was prepared from 5-aminoquinoline, 1,1'-carbonyldiimidazole, 6-methyl-(2,3-dihydropyrrolo-[3,2-e]indole)hydrochloride (D10) and triethylamine, in 42% yield, m.p. >240° C.

NMR(D_6-DMSO)δ: 3.35 (2H, t, J 7), 3.75 (3H, s), 4.38 (2H, t, J 7), 6.30 (1H, d, J 4), 7.19 (1H, d, J 8), 7.30 (1H, d, J 4), 7.50-7.58 (1H, m), 7.62 (1H, d, J 7), 7.75 (1H, t, J 7), 7.83-7.93 (2H, m), 8.45 (1H, d, J 7), 8.70 (1H, s), 8.92 (1H, d, J 4).

Found: C, 73.6; H, 5.50; N, 16.3
$C_{21}H_{18}N_4O$ requires C, 73.7; H, 5.3; N, 16.4
Found: M^+ 342, $C_{21}H_{18}N_4O$ requires 342

Example 18

6-Methyl-3-(3-quinolinylcarbamoyl)-2,3-dihydropyrrolo [3,2-e]indole (E18)

The title compound was prepared from 3-aminoquinoline, 1,1'-carbonyl diimidazole, 6-methyl-(2,3-dihydropyrrolo-[3,2-e]-indole hydrochloride (D10) and triethylamine in 53% yield, m.p. 222-4° C.

NMR(D_6-DMSO)δ: 3.35 (2H, d, J 7), 3.78 (3H, s), 4.32 (2H, d, J 7), 6.30 (1H, d, J 4), 7.25 (1H, d, J 8), 7.32 (1H, d, J 4), 7.50-7.68 (2H, m), 7.83-8.00 (3H, m), 8.54 (1H, d, J 4), 8.82 (1H, s), 9.05 (1H, s)

Found:C, 72.9; H, 5.5; N, 16.2,
$C_{21}H_{18}N_4O.^1/_4 H_2O$ requires C, 72.7; H, 5.3; N, 16.2
Found: M^+ 342, $C_{21}H_{18}N_4O$ requires 342

Example 19

5-Methyl-1-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E19)

The title compound was prepared from 2-methyl-4-aminoquinoline, 1,1'-carbonyl diimidazole and 5-methyl-(2,3-dihydropyrrolo[2,3-f]indole) (D6), in 57% yield, m.p.>240° C.

NMR (D_6-DMSO)δ: 2.64 (3H, s), 3.30 (2H, t, J 7), 3.72 (3H, s), 4.38 (2H, t, J 7), 6.3 (1H, d, J 4), 7.20 (1H, d, J 4), 7.30 (1H, s), 7.53 (1H, t, J 7), 7.70 (1H, t, J 7), 7.78 (1H, s), 7.90 (1H, d, J 7), 8.08 (1H, s), 8.15 (1H, d, J 7), 8.73 (1H,s)

Example 20

6,8-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole (E20)

6-Methyl-8-(N,N-dimethylaminomethyl)-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo [3,2-e] indole (D40) (0.5g, 0.0014 moles) was hydrogenated at STP in ethanol (50ml) over 10% palladium on charcoal catalyst (0.5g) for 24hrs then at 50p.s.i. for 4hrs. Filtration through kieselguhr followed by evaporation to dryness gave the crude product. Flash chromatography on silica gel eluting with 0-5% methanol/dichloromethane followed by recrystallisation from ethyl acetate/methanol give the title compound (E20) (0.174g, 40%) as white crystals. m.p. 228-230°C.

NMR (D_6-DMSO) δ: 2.32 (3H, s), 3.55 (2H, t, J=8Hz), 3.65 (3H, s), 4.21 (2H, t, J=8Hz), 7.00 (1H, s), 7.10 (1H, d, J=8Hz), 7.24-7.33 (1H, m), 7.83 (1H, d, J=8Hz), 7.94-8.03 (1H, m), 8.19 (1H, d, J=4Hz), 8.57 (1H, s), 8.73 (1H, d, J=3Hz).

Found: C, 69.77; H, 6.00; N, 18.08%
$C_{18}H_{18}N_4O\ ^1/_5H_2O$ requires: C, 69.77, H, 5.94; N, 18.09%

Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 21

6-Methyl-3-(3-pyridylcarbamoyl)-2,3,7,8-tetrahydropyrrolo[3,2-e]-indole (E21)

6-Methyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo [3,2-e]indole (E2) (1.0g, 0.0034 moles) was dissolved in glacial acetic acid (25ml) and treated with sodium cyanoborohydride (1.0g, 0.016 moles) at ambient temperature. The mixture was stirred for 4 hrs then diluted with water (100ml). The mixture was basified with 10% aqueous sodium hydroxide and the product extracted into dichloromethane, drying with sodium sulphate. Evaporation of the solvent followed by flash chromatography on silica gel eluting with 0-5% methanol/dichloromethane gave a white solid residue. Recrystallisation from ethyl acetate/60-80 petrol gave the title compound (E21) as white crystals (0.68g, 67%) m.p. 201-203°C.

NMR (D_6-DMSO) δ: 2.75 (3H, s), 2.89 (2H, t, J=8Hz), 3.15 (2H, t, J=8Hz), 3.31 (2H, t, J=8Hz), 4.22 (2H, t, J=8Hz), 6.40 (1H, d, J=7Hz), 7.33- 7.45 (1H, m), 7.70 (1H, d, J=7Hz), 8.03-812 (1H, m), 8.30 (1H, d, J=4Hz), 8.65 (1H, s), 8.85 (1H, d, J=4Hz).

Found: C, 69.07; H, 6.29; N, 18.90%, $C_{17}H_{18}N_4O$ requires C, 69.37; H, 6.16; N, 19.03%
Found: M^+ 294, $C_{17}H_{18}N_4O$ requires 294

Example 22

5-Methyl-1-(2-pyrazinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E22)

The title compound was prepared from 2-aminopyrazine anion (prepared using sodium hydride), 1,1'-carbonyldiimidazole, and 5-methyl-2,3-dihydropyrrolo[2,3-f]indole in dimethylformamide using a procedure similar to that described for Example 5, in 75% yield, m.p. 196-198°C.

NMR (D_6DMSO) δ: 3.26 (2H, t, J=10), 3.76 (3H, s), 4.25 (2H, t, J=10), 6.33 (1H, d, J=3), 7.20 (1H, d, J=3), 7.28 (1H, s), 8.07 (1H, s), 8.28 (1H, d, J=2), 8.37 (1H, d, J=2), 9.19 (1H, m), 9.38 (1H, s).

Found: C, 65.55; H, 5.36; N, 23.54%, $C_{16}H_{15}N_5O$ requires C, 65.52; H, 5.15; N, 23.88%
Found: M^+ 293, $C_{16}H_{15}N_5O$ requires 293

Example 23

2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[3,2-e]indole (E23)

To an ice-cooled solution of carbonyldiimidazole (CDI) (0.445g, 2.75 mmol) in dichloromethane (15ml) was added a solution of 5-amino-3-methylisothiazole hydrochloride (0.38g, 2.5mmol) and triethylamine (0.35ml, 2.5 mmol) in dichloromethane (15ml). The mixture was stirred for 1h at 0°C, then evaporated to dryness. The residue was dissolved in dimethyl formamide (DMF) (15ml) and to this solution was added dihydropyrroloindole hydrochloride (D10) (0.52g,2.5mmol) and triethylamine (0.35ml) in DMF (2.5ml). The mixture was heated at approx. 130°C, with stirring, for 1h, then cooled and poured into water. Solid product was filtered off, washed with water and dried, then triturated with dichloromethane/methanol. Trituration liquor was concentrated, with addition of petrol, to give a precipitate which was filtered off and combined with the trituration residue. Drying *in vacuo* gave the title compound, (0.42g, 54%) m.p. >250°C.

NMR (D_6-DMSO) δ: 2.29 (3H, s), 3.33 (2H, t, J=7), 3.75 (3H, s), 4.20 (2H, t, J=7), 6.29 (1H, d, J=4), 6.74 (1H, s), 7.25 (1H, d, J=9), 7.32 (1H, d, J=4), 7.90 (1H, d, J=9), 10.41 (1H, s).

Found: C, 61.13; H, 5.16; N, 17.84%, $C_{16}H_{16}N_4OS$ requires C, 61.52; H, 5.16; N, 17.93%

Example 24

2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[2,3-f]indole (E24)

The title compound was prepared by the method of E23, using 5-amino-3-methylisothiazole hydrochloride (0.60g, 4 mmol), CDI (0.71g, 4.4 mmol), triethylamine (0.56ml, 4 mmol) and dihydropyrroloindole (D6) (0.69g, 4 mmol). Triethylamine was added only with the isothiazole hydrochloride.
After pouring the final mixture into water and filtering off the product, the crude material was recrystallised from dichloromethane/methanol/petrol to give the title compound (0.76g, 61%), m.p. 254-255°C.

NMR (D_6-DMSO) δ: 2.30 (3H, s), 3.30 (2H, t, J=7), 3.74 (3H, s), 4.14 (2H, t, J=7), 6.35 (1H, d, J=4), 6.76 (1H, s), 7.20 (1H, d, J=4), 7.29 (1H, s), 8.08 (1H, s), 10.48 (1H, s).

Found: C, 61.31; H, 5.24; N, 17.74%. $C_{16}H_{16}N_4OS$ requires: C, 61.52, H, 5.15; N, 17.93%

Example 25

2,3-Dihydro-5-methyl-1-(5-quinolylcarbamoyl)-1H-pyrrolo[2,3-f]indole (E25)

The title compound was prepared by the method of E23, using 5-aminoquinoline (0.58g, 4 mmol), CDI (0.71g, 4.4 mmol), and dihydropyrroloindole (D6) (0.69g, 4 mmol). No triethylamine was used, and the initial reaction mixture was stirred for 1h at 0°C and 0.5h at room temperature.

After pouring the final mixture into water and filtering off the product, the crude material was recrystallised from dichloromethane/methane/petrol to give the title compound (0.48g, 35%), m.p. 240-243°C.

NMR (D_6-DMSO) δ: 3.43 (2H, t, J=8), 3.84 (3H, s), 4.42 (2H, t, J=8), 6.37 (1H, d, J=4), 7.27 (1H, d, J=4), 7.38 (1H, s), 7.63 (1H, dd, J=8.5), 7.72 (1H, d, J=8), 7.87 (1H, t, J=8), 7.99 (1H, d, J=8), 8.08 (1H, s), 8.55 (1H, d, J=8), 8.84 (1H, s), 9.00 (1H, d, J=5).

Found: C, 72.85; H, 5.45; N, 16.36%, $C_{21}H_{18}N_4O$ requires C, 73.67; H, 5.30; N, 16.36%

Example 26

2,3-Dihydro-5-methyl-1-(3-methyl-5-isoxazolylcarbamoyl)-1H-pyrrolo[2,3-f]indole (E26)

To a suspension of sodium hydride (80% in oil, 40mg, 1.33 mmol) in dry DMF (10ml) was added 5-amino-3-methylisoxazole (0.12g, 1.24 mmol), and the mixture was stirred for 20 min at 0°C. Imidazolylcarbamoyl pyrroloindole (D41) (0.32g, 1.20 mmol) was then added and the mixture was stirred for 1.5h at 100-130°C, then cooled and poured into water. The precipitate was filtered off, washed with water and dried to give the title compound (0.17g, 48%), m.p. 212-215°C.

NMR (D_6-DMSO) δ: 2.19 (3H, s), 3.24 (2H, t, J=7), 3.73 (3H, s), 4.14 (2H, t, J=7), 6.07 (1H, s,), 6.33 (1H, d, J=4), 7.20 (1H, d, J=4), 7.28 (1H, s), 8.05 (1H, s), 10.20 (1H, s).

Found: C, 64.83; H, 5.51; N, 18.83%, $C_{16}H_{16}N_4O_2$ requires: C, 64.85; H, 5.44; N, 18.91%

Example 27

N-(5-Isoquinolyl)-5-methyl-2,3-dihydropyrrolo[2,3-f] indole-1-carboxamide (E27)

The title compound was prepared from 5-aminoisoquinoline, carbonyl diimidazole and 1-amino-5-methyl- 2,3-dihydropyrrolo [2,3-f]indole, using a procedure similar to that described for Example 25, in 15% yield, m.p. 245-250°C.

NMR (D_6 DMSO) δ: 3.48 (2H, t, J=6), 3.86 (3H, s), 4.42 (2H, t, J=6), 6.38 (1H, d, J=2), 7.28 (1H, d, J=2), 7.40 (1H, s), 7.80 , (1H, t, d=6), 7.91 (1H, d, J=6), 7.99 (1H, d, J=6), 8.08 (2H, d, J=6), 8.60 (1H, d, J=6), 8.79 (1H, s), 9.42 (1H, s).

Found: M^+ 342.40, $C_{21}H_{18}N_4O$ requires 342.40

Example 28

N-(6-Quinolyl)-5-methyl-2,3-dihydro-pyrrolo [2,3-f]indole-1-carboxamide (E28)

The title compound was prepared from 6-aminoquinoline, carbonyl diimidazole, and 1-amino-5-methyl-2,3-dihydro-pyrrolo [2,3-f] indole using a procedure similar to that described for Example 25, in 12% yield, m.p. 217-220°C.

NMR (D_6 DMSO) δ: 3.30 (2H, t, J=6), 3.74 (3H, s), 4.23 (2H, t, J=6), 6.32 (1H, d, J=2), 7.20 (1H, d, J=2), 7.29 (1H, s), 7.42-7.49 (1H, m), 7.94 (2H, s),8.09 (1H, s), 8.27 (2H, m), 8.74-8.79 (2H, m).

Found: M^+ 342-40, $C_{21}H_{18}N_4O$ requires 342.40

Example 29

2-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]-indole (E29)

Nicotinoyl azide (0.142g, 0.96 mmol) was stirred at reflux under Ar in dry toluene (40 ml) for 1h, allowed to cool and 2-methyl-2,3-dihydropyrrolo[2,3-f]indole (D47) (0.15g, 0.87 mmol) in dry toluene (10 ml) was added. The solution was stirred for 1 h, the resulting precipitate filtered off, washed with a small quantity of Et_2O and dried thoroughly to afford the title compound (E29) (70 mg, 28%).

NMR (D_6-DMSO) δ : 1.25 (3H, d), 2.75 (1H, d), 3.46 (1H, dd), 4.82 (1H, m), 6.32 (1H, s), 7.20 (1H, s), 7.33 (1H, dd), 8.01 (1H, m), 8.01 (1H, s), 8.21 (1H, d), 8.68 (1H, s) 8.78 (1H, d), 10.83 (1H, bs, NH).

Found: C, 69.69; H, 5.71; N, 19.16%
$C_{17}H_{16}N_4O$ requires C, 69.85; H, 5.52; N, 19.16%
Found: M^+ 292 $C_{17}H_{16}N_4O$ requires 292

Example 30

2,5-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-*f*]-indole (E30)

Nicotinoyl azide (28.7 mg, 1.1 eq.) was stirred at reflux under Ar in dry toluene (40 ml) for 1h, allowed to cool and 2,5-dimethyl-2,3-dihydropyrrolo[2,3-f]indole (D49) (0.37g, 1.76 mmol) in dry toluene (10 ml) added. The solution was stirred for 1h, the solution evaporated to dryness, and purified by column chromatography (SiO_2, $CHCl_3$/MeOH 9:1) to afford the product as a pale yellow oil which was triturated with Et_2O to give a pale yellow solid (170 mg).

NMR ($CDCl_3$) δ : 1.33 (3H, d), 2.89 (1H, d), 3.62 (1H, dd), 3.84 (3H, s, NMe), 4.96 (1H, m), 6.42 (1H, d), 7.30 (1H, d), 7.39 (1H, s), 7.42 (1H, dd), 8.08 (1H, s), 8.13 (1H, s), 8.32 (1H, d), 8.80 (1H, s), 8.85 (1H, s, NH).

Found: C, 69.98; H, 6.11; N, 17.72%
$C_{18}H_{18}N_4O$ $^1/_6$ H_2O requires C, 69.90; H, 6.04; N, 18.10%
Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306.

Example 31

5-Ethyl-1-(3-pyridylcarbamoyl) 2,3,6,7-tetrahydropyrrolo-[2,3-f]indole (E31)

5-Ethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo-[2,3-f]indole (E 10) (0.7g, 0.0023 moles) was dissolved in glacial acetic acid (15 ml) and treated with sodium cyanoborohydride (0.72g, 0.0114 moles) at ambient temperature with stirring. The mixture was stirred for 1 h then diluted with water (100 ml), basified with 10% aqueous sodium hydroxide and extracted with dichloromethane (2x 100 ml). The organic solution was dried (Na_2SO_4), filtered and evaporated to dryness. Flash chromatography on silica gel eluting with 2-5% methanol/dichloromethane followed by recrystallisation of the solid obtained from ethyl acetate/40-60 petrol gave the title compound (E31) as a white crystalline solid (0.45 g, 64%) m.p. 151-153° C.

NMR (D_6-DMSO) δ : 1.10 (3H, t, J 7), 2.81 (2H, t, J 7), 2.98-3.11 (4H, m), 3.21 (2H, t, J 7), 4.07 (2H, t, J 7), 6.41 (1H, s), 7.29 (1H, q, J 5), 7.62 (1H, s), 7.93-7.96 (1H, m), 8.19 (1H, d, J 2), 8.51 (1H, s), 8.70 (1H, s).

Found: C, 69.56; H, 6.50; N, 18.04%
$C_{18}H_{20}N_4O$. 1/8 H_2O requires: C, 69.58; H, 6.57; N, 18.03%
Found: M^+ 308, $C_{18}H_{20}N_4O$ requires 308

Example 32

5-Methyl-1-(2-methyl-4-quinolinylcarbamoyl)-2,3,6,7-tetrahydropyrrolo[2,3-f]indole (E32)

5-Methyl-1-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E 19) (0.7 g, 0.002 moles) in glacial acetic acid (15 ml) was treated with sodium cyanoborohydride (0.58 g, 0.009 moles) as in the method of Example 9 to give the title compound (E32) as pale yellow crystals (0.44g, 63%) m.p. 242-244° C.

NMR (D_6-DMSO) δ : 2.61 (3H, s), 2.69 (3H, s), 2.80 (2H, t, J 7),3.10-3.22 (4H, m), 4.29 (2H, t, J 7), 6.45 (1H, s), 7.45-7.53 (1H, m), 7.64-7.77 (3H, m), 7.88 (1H, d, J 8), 8.12 (1H, d, J 8), 8.54 (1H, s)

Found: C, 72.69; H, 6.37; N, 15.36%
$C_{22}H_{22}N_4O$ 1/4 H_2O requires: C, 72.83; H, 6.21; N, 15.45%
Found: M^+ 358, $C_{22}H_{22}N_4O$ requires 358

Example 33

5-Methyl-1-(2-methyl-4-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole (E33)

The **title compound** was prepared from 2-methyl-4-aminopyridine anion (prepared using sodium hydride) 1,1'-carbonyldiimidazole, and 5-methyl-2,3-dihydropyrrolo[2,3-f]indole in dimethylformamide using a procedure similar to that described for Example 5, in 45% yield.

NMR (D_6-DMSO) δ : 2.40 (3H, s), 3.27 (2H, t, J 7), 3.72 (3H, s), 4.18 (2H, t, J 7), 6.32 (1H, d, J 3), 7.19 (1H, d, J 3), 7.26 (1H, s), 7.43 (1H, d, J 8), 7.50 (1H, s), 8.05 (1H, s), 8.22 (1H, d, J 8), 8.74 (1H, s).

Found: M^+ 306, $C_{18}H_{18}N_4O$ requires 306

Example 34

Pharmaceutical compositions for oral administration may be prepared by combining the following:

1) **Solid Dosage Formulation**

	% w/w
Compound of formula 1	10%
Magnesium stearate	0.5%
Starch	2.0%
HPM cellulose	1.0%
Microcrystalline cellulose	86.5%

The mixture may be compressed to tablets, or filled into hard gelatin capsules.
The tablet may be coated by applying a suspension of film former (e.g. HPM cellulose), pigment (e.g. titanium dioxide) and plasticiser (e.g. diethyl phthalate) and drying the film by evaporation of the solvent. The film coat can comprise 2.0% to 6.0% of the tablet weight, preferably about 3.0%.

2) **Capsule**

	%w/w
Compound of formula 1	20%
Polyethylene glycol	80%

The medicinal compound is dispersed or dissolved in the liquid carrier, with a thickening agent added, if required. The formulation is then enclosed in a soft gelatin capsule by suitable technology.

Example 35

A pharmaceutical composition for parenteral administration may be prepared by combining the following:

	Preferred Level
Compound of formula 1	1.0%
Saline	99.0%

The solution is sterilised and sealed in sterile containers.

Pharmacological Data

[^{3}H]-mesulergine binding to rat or human 5-HT$_{2C}$ clones expressed in 293 cells in vitro

Evidence from the literature suggests that 5-HT$_{2C}$ antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT$_{2C}$ binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine from 5-HT$_{2C}$ clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos et al, 1984.

The cells suspension (400ml) was incubated with [^{3}H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10^{-6}M). Ten concentrations of test drug (3×10^{-9} to 10^{-4}M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC_{50} values were determined using a four parameter logistic program (DeLean 1978) and the pK_i (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

K_i = inhibition constant.

C = concentration of [^{3}H]-mesulergine

Kd = Affinity of mesulergine for 5-HT$_{2C}$ binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

Julius *et al.* (1988) Science 241, 558-564

DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

Results: The compound of examples 1 to 11 have pK_i values of 6.04 to 9.29.

Reversal of MCPP-induced Hypolocomotion

Administration of m-(chlorophenyl)piperazine (mCPP) to rats induces hypolocomotion (Kennett and Curzon 1988, Luckie *et al.* 1989) as seen with the related drug 1-(m-trifluoromethylphenyl)piperazine (TFMPP) (Lucki and Frazer 1982, Kennett and Curzon 1988). This effect was blocked by the non specific 5-HT_{2C}/5-HT_{2A} receptor antagonists mianserin, cyproheptadine and metergoline and perhaps by mesulergine. It was not blocked by the 5-HT_{2A} receptor antagonists ketanserin and ritanserin at relevant doses (Kennett and Curzon 1991) nor by antagonists of 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, α_2 adrenoceptors or dopamine D_2 receptors. The effect of mCPP is therefore considered to be mediated by 5-HT_{2C} receptors (Kennett and Curzon 1988) as confirmed by subsequent studies (Lucki *et al.*, 1989). Since mCPP causes hypolocomotion when infused into the cerebral ventricles this effect is probably centrally mediated (Kennett and Curzon 1988).

mCPP-induced hypolocomotion was measured in automated locomotion cages of dimensions 56 cm long x 16½ cm wide x 25 cm high and made of black perspex. Two photobeams traversed the width of the cages at either end at ground level. Sequential breaking of these beams allowed the measurement of cage transits.

Male Sprague Dawley rats (200-250g) (Charles River) were housed in groups of six. They were given drugs orally 1h pretest and 40 mins later mCPP (7 mg/kg i.p.). After a further 20 min they were placed in individual automated cages in groups of four under red light in an adjacent room. After 10 min the test was terminated. Reversal of mCPP-induced hypolocomotion was considered as evidence of *in vivo* central 5-HT_{2C} receptor antagonist properties.

Kennett, G.A., Curzon, G., (1991). Brit. J. Pharmacol. 103, 2016-2020.

Lucki, I., Frazer, A., (1982). Am. Soc. Neurosci. 8 (abstr), 101.

Lucki, I., Ward, H.R., Frazer, A., (1989). J. Pharmacol. Exp. Therap. 249, 155-164.

Results: The compounds of examples 1, 2 and 4 had ID_{50}'s of 5.5 to 22.3mg/kg p.o.

Social Interaction Test

Potential anxiolytic properties have been evaluated using the social interaction test based on that described by File (1980 J.Neurosci.Meth., 2, 219). Active social interaction between male rats is usually quantitated by counting interactive behaviours such as following, grooming, sniffing, climbing over or under, biting, mounting and boxing. This behaviour is supressed when the rats encounter each other in an environment which is novel and brightly lit. Under these circumstances anxiolytic drugs will enhance the level of social interaction.

Rats were housed in groups of 8 in a holding room adjacent to the experimental chamber for 8 days. They were then housed singly in the same room for 3 days prior to the experimental day. On the experimental day rats were injected p.o. 1h pretest with vehicle or drug in pairs at 15 min intervals beginning at 10.00 am. 60 Mins later they were placed with a weight matched pair mate (encountered for the first time) in the social interaction box in a separate room. The box was made of white perspex 54 x 37 x 26 cm with no lid. The floor was divided into 24 equal squares and the cage was brightly lit. Active social interaction was scored blind over the next 15 min by remote video monitoring to give total interaction scores. The number of squares crossed by each rat was also scored and summed. At the end of each test the box was carefully wiped with a damp cloth. Unlike anxiolytic drugs, treatments that enhance social interaction by stimulant action will also increase locomotion. Treatments that are sedative reduce locomotion.

The compound of Example 2 showed a significant increase in social interaction at doses of 10 mg/kg.

Geller-Seifter Procedure

Potential anxiolytic properties are evaluated using the Geller-Seifter procedure based on that originally described by Geller and Seifter, (1960) Psychopharmacologia, 1, 482-492. This procedure has been shown to be selective for drugs with anxiolytic properties (Cook and Sepinwall, (1975) "Mechanism of Action of Benzodiazepines" ed. Costa, E. and Greengard, P., Raven Press, New York, pp. 1-28).

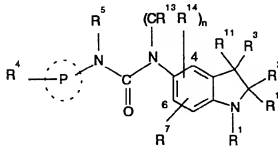
Rats are trained on a variable interval 30 sec schedule (VI30) to press a lever in order to obtain food reward. The 5 min sessions of the VI30 schedule alternate with 2-5 min of a schedule (FR5) in which every 5th lever press is followed by presentation of a food pellet paired with a 0.5 sec mild footshock. The total study lasts approximately 30 mins. Rats typically respond with high rates of lever pressing under the VI30 schedule and low response rates under the FR5 'conflict' session. Anxiolytic drugs increase the suppressed response rates of rats in a 'conflict' session.

Drugs are administered intraperitoneally or orally to groups of 3-8 rats 30 min before testing. The results are expressed as the percentage increase in the square root of the total number of lever presses in the FR5 'conflict' session. Square root transformation is necessary to normalise the data for statistical analysis using parametric methods.

The compound of Example 2 showed a significant increase in responding in the 'conflict' session at dose levels in the range 5 mg/kg p.o.

Claims:

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain;

R^4 is hydrogen, C_{1-6} alkyl, halogen, NR^8R^9 or OR^{12}, where R^8, R^9 and R^{12} are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl;

n is 2 or 3; and

the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl.

2. A compound according to claim 1 in which R^1 is methyl or ethyl.

3. A compound according to claim 2 in which R^2 and R^3 are hydrogen and R^{10} and R^{11} together form a bond.

4. A compound according to claim 3 in which R^4 is hydrogen or methyl.

5. A compound according to claim 4 in which R^5 and R^7 are hydrogen.

6. A compound according to claim 5 in which $(CHR^{13})_n$ is an ethylene group.

7. A compound according to claim 1 which is selected from:

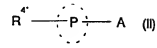
5-Methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6-Methyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
5,7-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6-Methyl-3-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
6-Methyl-3-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
5-Methyl-1-(2-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-Methyl-1-(4-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-Methyl-1-(3-pyridylcarbamoyl)-2,3,6,7-tetrahydropyrrolo[2,3-f]indole
5-Ethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5-n-Propyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
5,6-Dimethyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole
6,7-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole
1-Methyl-N-(3-pyridyl)-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline-5-carboxamide
3-Methyl-N-(3-pyridyl)-6,7,8,9-tetrahydro-3H-pyrrolo[3,2-f]quinoline-6-carboxamide
6-Methyl-3-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole,
6-Methyl-3-(5-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole,
6-Methyl-3-(3-quinolinylcarbamoyl)-2,3-dihydropyrrolo [3,2-e]indole,
5-Methyl-1-(2-methyl-4-quinolinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole,
6,8-Dimethyl-3-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[3,2-e]indole,
6-Methyl-3-(3-pyridylcarbamoyl)-2,3,7,8-tetrahydropyrrolo[3,2-e]-indole,
5-Methyl-1-(2-pyrazinylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[3,2-e]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isothiazolylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(5-quinolylcarbamoyl)-1H-pyrrolo[2,3-f]indole,
2,3-Dihydro-5-methyl-1-(3-methyl-5-isoxazolylcarbamoyl) -1H-pyrrolo[2,3-f]indole,
N-(5-Isoquinolyl)-5-methyl-2,3-dihydropyrrolo[2,3-f] indole-1-carboxamide,
N-(6-Quinolyl)-5-methyl-2,3-dihydro-pyrrolo [2,3-f]indole-1-carboxamide;
or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

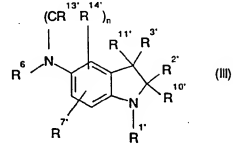
10. A process for the preparation of a compound of formula (I) or a salt thereof, which process comprises:

(a) the coupling of a compound of formula (II);



(II)

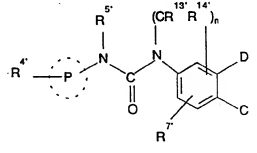
with a compound of formula (III);



(III)

wherein A and R^6 contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is R^5 as defined in formula (I) or a group convertible thereto, n is as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ are R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4 and R^7 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5, and R^7 respectively to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt thereof;

or (b) cyclising a compound of formula (IV):



(IV)

wherein $R^{4'}$, $R^{5'}$, $R^{7'}$, $R^{13'}$ and $R^{14'}$ are as defined in formulae (II) and (III), n is as defined in formula (I), and C and D contain the appropriate functional group(s) necessary to form the indole or indoline ring substituted by $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$ and $R^{11'}$ as defined in

(III), and thereafter optionally and as necessary in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{10'}$, $R^{11'}$, $R^{13'}$, $R^{14'}$, $R^{4'}$, $R^{5'}$ and $R^{7'}$ when other than R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, to R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, interconverting R^1, R^2, R^3, R^{10}, R^{11}, R^{13}, R^{14}, R^4, R^5 and R^7, and forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

PCT/EP 93/02031

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; A61K31/395; C07D471/04; //(C07D487/04, 209:00,209:00)(C07D471/04,221:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	WO,A,9 205 170 (BEECHAM GROUP PLC) 2 April 1992 cited in the application see claims -----	1,9

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 SEPTEMBER 1993	25. 11. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9302031
SA 77625

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 30/09/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9205170	02-04-92	AU-A- 8503891	15-04-92
		CA-A- 2091246	14-03-92
		EP-A- 0550507	14-07-93